ACP | MKSAP® 19

Medical Knowledge Self-Assessment Program®

Oncology

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Leading Internal Medicine, Improving Lives

Welcome to the Oncology Section of MKSAP 19!

In these pages, you will find updated information on issues in oncology; breast, ovarian, and cervical cancers; gastroenterological malignancies; lung cancer; lymphoid malignancies; melanoma; the effects of cancer therapy and survivorship; and other topics in oncology. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of oncology.

MKSAP 19 strives to provide the clinical knowledge its learners need to navigate their longitudinal learning paths. MKSAP 19's core content contains essential, newly researched information in 11 subspecialty areas of internal medicine—created by dozens of expert generalists and subspecialists. Development of MKSAP 19's syllabus and its 1200 all-new, peer-reviewed, psychometrically validated multiple-choice questions (MCQs) has been informed by ABIM Certification and Maintenance of Certification (MOC) requirements, emerging internal medicine knowledge, and our learners' feedback. MKSAP 19 continues to include *High Value Care* (HVC) recommendations and MCQs, based on the concept of balancing clinical benefit with costs and harms. Hospital-based internists can continue to trust that MKSAP's comprehensive hospitalist content, integrated throughout the syllabus, and hospitalist-focused MCQs, specially designated with the blue hospitalist icon (H), continue to align with the ABIM's Focused Practice in Hospital Medicine MOC exam blueprint and enhance learning for hospital-based practitioners.

More than ever before, MKSAP 19 Digital focuses on individualized learning and convenience. In addition to custom quizzes and interlinked questions and syllabus sections, MKSAP 19 Digital's new learning dashboard enables users to create a self-directed learning plan, with topic-specific links to resources within MKSAP and ACP Online. Multimedia formats, including whiteboard animations and clinical videos, will benefit our audiovisual learners, while MKSAP's Earn-as-You-Go CME/MOC feature now allows subscribers to earn CME/MOC as they answer individual questions. In addition to Extension Questions and New Info Updates, MKSAP 19 Complete and Complete Green continue to offer Virtual Dx and Flashcards and now offer brand-new enhancements: MKSAP Quick Qs, a set of concise questions mapped to high-frequency/high-importance areas of the ABIM blueprint mirroring boards-style MCQs, and an embedded digital version of Board Basics for easy-access exam prep.

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On behalf of the many internists and editorial staff who have helped us create our new edition, we are honored that you have chosen to use MKSAP 19 to meet your lifelong learning needs.

Sincerely,

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The learning objectives of MKSAP 19 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked or confusing
- Improve clinical management decisions that affect patient safety and quality of care
- Determine when to refer patients for care by medical subspecialists, surgeons, and other members of the health care team
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internal medicine specialists, including primary care physicians and hospitalists
- Internal medicine subspecialists who desire to remain up to date in internal medicine
- Residents preparing for the ABIM Internal Medicine Certification Examination
- Physicians engaged in the ABIM Maintenance of Certification Longitudinal Assessment Option, preparing for the ABIM Internal Medicine Maintenance of Certification Examination, or engaged with the ABIM Focused Practice in Hospital Medicine program

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High Value Care Key Points

Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [**HVC**].

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Errata and Revisions for MKSAP 19 will be available through MKSAP 19 Digital at mksap19.acponline.org as new information becomes known to the editors.

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Oncology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 19 in several important ways. MKSAP 19 includes HVC-identified key points in the text, HVC-focused multiple-choice questions, and, in MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Oncology section of MKSAP 19.

- Imaging studies such as PET, CT, or bone scan for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.
- Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.
- Neither radiation therapy nor hormonal therapy provides benefit after bilateral mastectomy for patients with ductal carcinoma in situ (see Item 70).
- Multigene recurrence assays or gene expression profiles have dramatically improved the ability to avoid chemotherapy for patients at low risk of recurrence who will not benefit from chemotherapy and to identify patients at greater risk who do benefit from chemotherapy (see Item 45).
- Consensus guidelines indicate that pregnancy after breast cancer should not be discouraged (see Item 16).
- Second-look laparotomy to assess pathologic response following chemotherapy of ovarian cancer should not be performed.
- Annual cervical or vaginal cytology should be done on all cervical cancer survivors; additional surveillance imaging and laboratory studies for cervical cancer survivors are recommended only if there are signs or symptoms suggestive of recurrence.
- PET scans should not be used for preoperative staging or postoperative surveillance in colorectal cancer.
- PET scans do not add value in the staging of pancreatic cancer and are not part of standard management.
- Well-differentiated neuroendocrine tumors are indolent and often initially only require observation and serial imaging.
- Anal cancer is often curable with combined irradiation and chemotherapy; surgery is typically not indicated (see Item 22).
- Patients with poor performance status and advanced non–small cell lung cancer without a driver mutation do not benefit from chemotherapy nor immunotherapy and are best served with supportive care (see Item 25).
- Routine imaging for head and neck cancer after a negative posttreatment scan is not indicated unless signs and symptoms suggest recurrent disease.
- Although patients who receive radiation therapy that includes the thyroid bed are at increased risk of thyroid cancer, screening thyroid ultrasonography is not indicated.
- In men with low-risk prostate cancer, active surveillance is a reasonable strategy because some men will never require treatment, and outcomes are no worse if men with low-grade cancer are treated at the time of progression rather than when first diagnosed (see Item 38).
- Patients with prostate-specific antigen–only recurrence of prostate cancer may be treated with androgen deprivation therapy, although observation is also a reasonable choice.
- Patients with CT findings pathognomonic for renal cell carcinoma do not need a biopsy to confirm the diagnosis.
- Chronic lymphocytic leukemia is typically an indolent disease, and many patients require no therapy for many years (see Item 49).
- Physical examination and PET/CT are used to stage patients with Hodgkin lymphoma; laparotomy and splenectomy are no longer performed.
- Chemotherapy without irradiation is a treatment option for early-stage Hodgkin lymphoma after a complete

metabolic response assessed by interim PET/CT after two to three cycles of treatment (risk-adapted therapy) (see Item 36).

- In patients with a metastatic cancer of unknown primary site, CT and histologic, endoscopic, and gender-specific cancer evaluations are reasonable; however, nonspecific tumor markers, PET, and gene expression arrays should not be done.
- Palliative or hospice care is appropriate for patients with an unfavorable subtype of cancer of unknown primary site who have comorbidities and poor performance status.
- Nodal metastases are uncommon in thin melanomas (Breslow depth less than 0.8 mm) and need not be assessed.
- Most patients with neutropenic fever should be managed with monotherapy with an antipseudomonal β-lactam agent.
- There is no better therapeutic success but rather an increased risk of toxicity from adding an aminoglycoside to a broad-spectrum β-lactam in the treatment of febrile neutropenia (see Item 33).
- Growth factors are not routinely used in the treatment of patients with neutropenic fever unless the patient has severe neutropenia ($<100/\mu L$ [$0.1 \times 10^9/L$]) expected to last more than 10 days or has other high-risk features.
- Loop diuretics are not indicated in the treatment of hypercalcemia of malignancy unless kidney failure or heart failure is present; in these circumstances, intravenous expansion of vascular volume should precede the administration of loop diuretics (see Item 43).
- Spinal cord compression from radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression; instead, patients may be treated urgently with radiation therapy alone (see Item 63).

Oncology

Issues in Oncology

Introduction

Medical oncology is undergoing constant change and improvement. Among the most important advances of the past decade has been the incorporation of immune checkpoint inhibitors into the standard treatment of many malignancies. These agents, although not directly attacking the patient's cancer, deactivate checkpoints that would otherwise suppress the immune system, and so facilitate the patient's own immune surveillance efforts to destroy the cancer. Another major advance includes the expanded role of molecular profiling and precision therapeutics. Current techniques allow for genomic profiling of tumor tissue, either from fresh biopsies, from archived, paraffin-embedded specimens, or from blood-based tumor mutation profiling. With the knowledge of the mutational profile, oncologists can make more informed decisions in the selection and rejection of different therapeutic options and inclusion of so-called targeted therapies that are designed to inhibit a particular molecular mutation or aberration. However, many traditional aspects of oncology, including the use of histologic diagnosis and clinical staging, as well as extensive use of cytotoxic chemotherapy, radiation therapy, and surgery, remain central to current oncologic practice. The cancer care continuum is now recognized to include not only diagnosis and treatment but also supportive/palliative care, survivorship care, and end-of-life care.

Careful clinical evaluation and staging, understanding and communicating realistic goals of care, and recognizing and promoting patient preferences remain central to the practice of oncology. Meaningful progress has been made in many types of cancer. However, most cancers, once metastasized, although treatable with substantial potential for improvements in overall survival and quality of life, are still incurable. Supportive management of adverse effects has also improved; however, the adverse effects of cancer chemotherapy remain problematic for many patients, and sensitivity to the risks versus benefits must be considered when discussing treatment options with patients. Burdensome increases in the cost of new oncology drugs has become a focus of concern. Some of these high-cost drugs are highly active and offer substantial benefits, whereas others result in survival advantages measured in months or even weeks that, although statistically significant, are of debatable clinical relevance. The impact of financial toxicity has become an important consideration in oncologic care.

Staging

To plan a treatment strategy, a clinician must first determine the stage, or extent, of the cancer. Early-stage cancers are often cured by local therapy, such as surgery or irradiation, whereas more advanced-stage cancers require a systemic approach. Solid tumors are staged using the TNM system. In the TNM system, *T* (T1-T4) refers to the size or extent of local invasion of the primary tumor, *N* (N0-N3) indicates locoregional lymph node involvement, and *M* indicates the absence (M0) or presence (M1) of distant metastases. Some hematologic (liquid) tumors have unique tumor-specific staging systems.

Appropriate imaging techniques depend on the expected behavior pattern of each cancer type and differ from one tumor type to the next. Therefore, a proper cancer evaluation requires knowledge of the specific disease entity so that the necessary tests can be done and unnecessary tests avoided. Tests with very low yield should not be ordered in the absence of specific directing symptoms. For example, bone and brain imaging is appropriate in the staging of patients with lung cancer because bone and brain metastases are common and may be asymptomatic. However, in patients with presumed locoregional colorectal cancer, asymptomatic bone or brain metastases are exceedingly rare; consequently, routine imaging of these sites is not warranted. Staging in a patient with cancer is generally the most accurate indicator of prognosis and largely dictates the therapeutic strategy.

KEY POINTS

- Most solid tumors are staged using the TNM cancer staging system, in which *T* represents the size or extent of local invasion of the primary tumor (T1-T4), *N* indicates locoregional lymph node involvement (N0-N3), and *M* indicates the absence (M0) or presence (M1) of distant metastases.
- Appropriate cancer-staging imaging techniques depend on the expected behavior pattern of each cancer type; therefore, proper cancer evaluation requires knowledge of the specific disease entity so that the necessary tests can be done and unnecessary tests avoided.
- Within a particular type of cancer, staging is generally the most accurate prognostic indicator and largely dictates the therapeutic strategy.

Performance Status

Performance status is a means of quantifying how medically fit a patient is. A good performance status predicts favorable tolerance and response to treatment. Patients with a poor performance status are much more likely to experience serious or life-threatening toxicity and much less likely to benefit from treatment.

It is important to differentiate patients with a poor performance status who are debilitated due to chronic comorbidities from patients who would otherwise be medically fit but are acutely debilitated by their cancer. The latter situation may warrant an attempt at aggressive treatment because reversing the cancer is the only strategy that will improve the patient's overall condition, whereas the former may need to be treated with less aggressive treatment or possibly no specific anticancer treatment. Cancer drug approvals are based on clinical trials, virtually all of which limit participants to patients with good performance status, so the degree to which the results of these trials are relevant to patients with poor performance status is limited.

Age alone should not be a reason to avoid aggressive treatment. Elderly patients who are otherwise medically fit and healthy and have a good performance status may tolerate aggressive therapy well.

The two most commonly used performance status scales are the Karnofsky Performance Scale and the Eastern Cooperative Oncology Group/World Health Organization system (also called the Zubrod scale). These are outlined and contrasted in **Table 1**.

KEY POINTS

- Patients with poor performance status may be divided into two groups: patients who are debilitated by chronic comorbidities and may need less aggressive treatment and those who are debilitated by the cancer but are otherwise medically fit and might benefit from aggressive treatment.
- Most clinical trials used to determine treatment efficacy and safety are based on patients with good performance status; the results of such trials should generally not be expected in patients with poor performance status.

Goals of Therapy

Clear and candid communication between clinicians and patients is essential for good oncologic care. When communicating treatment options and recommendations, clinicians must work to establish realistic treatment goals. When a cure is not realistically possible, goals such as lengthening survival, shrinking a tumor, controlling disease growth, palliation or preventing disease-related symptoms, and maintaining quality of life should be discussed. The potential benefits of treatment must be weighed and considered against their risks and toxicities. Patients with incurable cancer face choices of more aggressive therapy designed to prolong their life, associated

TABLE 1. Oncology Performance Status Systems

ECOG/WHO Performance Status[a]
0 - Fully active; no restrictions on activities
1 - Unable to do strenuous activities, but able to carry out office work, light housework, or sedentary activities
2 - Able to walk and manage self-care, but unable to work; out of bed or chair >50% of waking hours
3 - Confined to bed or chair >50% of waking hours; capable of limited self-care
4 - Moribund. Fully confined to a bed or chair; unable to do any self-care
5 - Death
Karnofsky Performance Status
100 - Normal; no symptoms or evidence of disease
90 - Minor symptoms, but able to carry on normal activities
80 - Some symptoms; normal activity requires effort
70 - Unable to carry on normal activities, but able to care for self
60 - Needs frequent care for most needs; some occasional assistance with self-care
50 - Needs considerable assistance with self-care and frequent medical care
40 - Disabled; needs special care and assistance
30 - Severely disabled; hospitalized
20 - Very ill; significant supportive care is needed
10 - Actively dying
0 - Death

ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization.

[a] Also called the Zubrod scale.

with more unpleasant and potentially dangerous adverse effects. Similarly, more aggressive initial therapy may result in prolonged remission or disease-free survival but may not necessarily change overall survival. All patients will have a unique perspective on how they interpret this equation.

A cancer diagnosis has been shown to be a leading cause of personal bankruptcy, and studies show financial worries contribute to patients' anxiety. Inability to meet copays or coinsurance requirements, especially for expensive oral anticancer medications, is a leading cause of failure to properly receive therapy. A clear understanding of the goals of care and the toxicities, including financial toxicity, is necessary for patients and physicians to make informed choices in treatment options. This concept of financial toxicity goes beyond individual patients in affecting the overall health care economy. Quantifying the overall benefit of extending a patient's life by relatively short periods (less than 2 months' median benefit) and contrasting that benefit by the financial cost of care require complex ethical, economic, and public health decisions.

Early-stage cancers often have a high chance of cure. With increasing cancer stage, the possibility of cure diminishes. Most metastatic cancers are treatable but not curable. The risks of treatment are higher and may outweigh the benefit in patients with poor performance status due to chronic medical comorbidities or those who have not been able to tolerate initial treatment attempts. For such patients or for those who have exhausted standard treatment options, supportive, comfort-oriented care may be most appropriate. Use of adequate analgesia, as well as involving supportive care specialists, is important throughout the continuum of care but particularly so in patients with pain or with symptoms from either disease or therapy. Studies suggest that such supportive care, when instituted early in conjunction with anticancer therapy, helps patients better tolerate their cancer care and should not be delayed to the point at which no more active cancer therapy is considered.

KEY POINTS

- The potential benefits of treatment must be weighed and discussed along with its risks and toxicities, including financial toxicity, because the costs of anticancer treatments have increased substantially.
- Palliative care should be instituted early in the management of patients with cancer and not reserved only for the time when they are no longer receiving cancer therapy.

Understanding Cancer Terminology

A clear understanding of cancer terminology is necessary to facilitate informed discussions and develop realistic treatment goals.

The one pure and simple term is *cure*. Cure means that the cancer is gone, no further treatment is required, and the patient can be expected to live out his or her life without seeing that cancer again. Cure should not be confused with the term *overall survival*, which is defined as the amount of time from the start of treatment until death. Overall survival is often misunderstood by patients to be synonymous with cure. Median survival outcomes that are reported in studies are too often explained to patients as indicating how long they will live, but it must be understood and explained that medians identify the center of an often-broad, bell-shaped curve, and may be meaningful for populations, but cannot predict an outcome for any one individual patient.

Patient expectations can be further confused by the frequent use of the phrase *significant improvement in survival*, in which *significant* refers to the statistical certainty of the finding but is often misinterpreted as a *substantial* improvement in survival. Many drugs have been approved with significant improvements in median survival that are limited to less than 2 or 3 months, a quantity that most would agree is not substantial. Furthermore, one must be cautious about interpreting nonrandomized comparisons of older versus newer survival data. Randomized controlled trials are the only reliable means of comparing one treatment with another.

One of the most misrepresented and misunderstood terms is *progression-free survival*. It is the time from when a treatment is started until that treatment is no longer controlling the cancer. The word *survival* was initially included in the term because the duration of progression-free survival is defined by either growth of the cancer (progression) or patient death, whichever occurs first; thus, the term has nothing to do with overall survival and is often confused with it. *Progression-free interval* would be a more apt term.

Response rate is the percentage of patients in a clinical trial whose tumors shrink to a prespecified degree (as indicated on imaging studies such as CT or MRI) with treatment. Response in hematologic malignancies is defined by other clinical criteria. Response rate may not correlate with overall survival, but there is a strong emotional benefit to patients when the tumor is regressing, and in symptomatic patients, such shrinkage is likely to alleviate or delay symptoms.

KEY POINTS

- An increase in overall survival is not synonymous with cure, median survival is only relevant to populations, and "significant" improvements reported in clinical trials do not necessarily mean substantial improvements.
- Progression-free survival measures the time from initiation of treatment until the cancer progresses or the patient dies; it would be better termed progression-free interval.

Treatment Approaches

The classic cancer treatment modalities are surgery, irradiation, and chemotherapy. As current technology has advanced, chemotherapy is best subdivided into the more classical cytotoxic chemotherapies, targeted or precision therapies, and immunotherapies.

Traditional Cancer Therapies

For tumors that are localized, surgical resection remains at the center of treatment. After a complete resection, the patient is at risk from microscopic tumors that may remain. Neoadjuvant (preoperative) or adjuvant (postoperative) treatment with irradiation, chemotherapy, or both may be used to eradicate residual microscopic disease and increase the chance for cure. The nature of the treatment, in terms of chemotherapy, irradiation, or both, depends on the type of tumor and its characteristic pattern of spread. Randomized trials are crucial in determining whether, for any given population of patients, neoadjuvant or adjuvant therapy improves an important outcome, such as cure, or disease-free interval, without unacceptable toxicity. Conversion therapy seeks to convert an unresectable tumor to one that is resectable by shrinking it away from critical structures and creating a plane for resection that was previously lacking. This type of treatment differs from neoadjuvant chemotherapy, which targets micrometastases of an already resectable tumor.

Balancing therapy efficacy and toxicity—in particular, the need for adjuvant or neoadjuvant therapy or the desired aggressiveness of the primary chemotherapy, radiation therapy, or surgical therapy for populations of patients—has traditionally been based on stage, pathology, and understanding the tumor's overall behavior. Currently available imaging and laboratory studies are somewhat limited in terms of their ability to identify which patients will be at risk for cancer recurrence after definitive surgery. Numerous tumor markers, gene panels, and other technologies are available, but few are definitive. The preferred assay would be predictive, meaning that it could identify the subset of patients at risk for recurrence who will benefit from an intervention such as adjuvant chemotherapy. An example of this is a commercially available 21-gene assay for breast cancer that identifies a patient population who is at risk for recurrence and will have that risk lowered by chemotherapy. Such predictive tools are highly useful because they provide actionable information in terms of who to treat and who not to treat. A similar multigene assay in colorectal cancer is prognostic in that it can quantitate a patient's risk of recurrence but fails to identify which patients will have their risk lowered by chemotherapy. Therefore, it does not provide information that is useful for decision making. Predictive tests are of high value in that they provide clear, actionable information. Prognostic tests add no value in dictating therapy, as they do not provide actionable information.

KEY POINTS

- Treatment with irradiation, chemotherapy, or both, in addition to definitive surgery, is called neoadjuvant if administered preoperatively or adjuvant if administered postoperatively.

(Continued)

KEY POINTS *(continued)*

- Predictive assays identify the subset of patients who will or will not benefit from an intervention, whereas prognostic assays can identify the subset of patients at higher or lower risk but do not offer guidance in selecting treatment to mitigate that risk.

Precision Medicine

Current developments in chemotherapy are centered on creating agents that target specific driver mutations in a particular cancer. Although in theory, these agents should be more selective and have fewer toxicities than older, conventional chemotherapies, this has not always turned out to be the case. Many of the signaling pathways that are hyperactive in tumor cells remain at least somewhat active in normal cells, and so disruption of these pathways can produce considerable adverse effects.

The goal of precision medicine is to identify specific mutations or alterations that are driving growth and survival in a particular tumor and to treat with agents designed to inhibit that aberrant pathway. Markers can be either inclusionary, in that they include a patient in a therapy that otherwise might not be considered, or exclusionary, in that they exclude a patient from a treatment that otherwise might have been used.

An example of an inclusionary marker is the V600 *BRAF* mutation in melanoma. Specific *BRAF* inhibitors, such as vemurafenib, dabrafenib, or encorafenib, would only be appropriate for use in melanomas that harbor this specific mutation. Melanomas lacking this mutation would not be treated with these agents. Trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (*HER2*) on the cell surface, is only active in breast or gastroesophageal tumors that overexpress *HER2*.

Examples of exclusionary markers are *RAS* mutations. The anti-epidermal growth factor receptor monoclonal antibodies cetuximab and panitumumab were initially thought to be appropriate for treatment of all colorectal cancers. Subsequently, it was determined that any tumors harboring mutations in either the *KRAS* or *NRAS* gene were not only highly resistant to responding to these agents, but in fact, the growth of the *RAS*-mutated tumors may even be accelerated by these agents. All metastatic colorectal cancers now require tumor genotyping for *KRAS*, *NRAS*, and *BRAF* mutations, and only tumors lacking all three of these mutations are appropriate for treatment with cetuximab or panitumumab.

Circulating tumor DNA can often be isolated from the blood of patients with metastatic cancer, and molecular profiling of the tumor can therefore be accomplished on a blood sample. This technique, referred to as a liquid biopsy, may be useful to avoid an unnecessary invasive procedure when archived tumor tissue is not available. Ongoing research will determine whether circulating tumor DNA may be useful either for surveillance after surgery or to identify at-risk patients for adjuvant therapy.

KEY POINTS

- Precision medicine refers to agents that target specific mutations or alterations that are driving growth and survival in a particular tumor.
- Tumor markers of mutations or alterations can be inclusionary, in that they include a patient in a therapy that otherwise might not be considered, or exclusionary, in that they exclude a patient from a treatment that otherwise might have been used.

Immunotherapy

Immunotherapy agents are drugs that do not attack the cancer directly but rather mobilize the patient's own immune system to do so. This has become possible through the identification of immune checkpoints, which serve as "brakes" on the immune system in order to prevent the immune system from attacking itself and causing autoimmune diseases. Antibodies that block these checkpoints release the brakes on the immune system and allow it to aggressively attack the tumor. Adverse effects are related to resultant autoimmunity from the less-regulated immune system and can be severe. The first immune checkpoint identified was the antigen-4 (A-4) molecule on the surface of the cytotoxic lymphocyte (T cell), hence its designation cytotoxic T-lymphocyte antigen-4. Antibodies that block cytotoxic T-lymphocyte antigen-4, such as ipilimumab, have been successful in mobilizing the immune system against melanoma, renal cell carcinoma, and other malignancies. The other immune checkpoint that has been successfully exploited is the programmed death 1 (PD-1) receptor. Anti-PD-1 agents, such as nivolumab or pembrolizumab, have shown substantial and durable activity against melanoma and non-small cell lung cancers, as well as other tumors. Agents against the ligand of PD-1, PD-L1, such as atezolizumab or durvalumab, have also shown important clinical activity. Combinations of these agents are showing further effectiveness but with increased toxicity and also considerable expense. Many other checkpoints in the immune system are now being explored by numerous drugs in development.

Further progress in immunotherapy has occurred in the use of cellular immunity, particularly the development and commercialization of chimeric antigen receptor T cells, which have demonstrated striking activity in selected B-cell leukemias and lymphomas, albeit with substantial clinical and financial toxicity. Investigations into development of this technology for other liquid and some solid tumors are ongoing.

KEY POINT

- Immune checkpoints prevent the immune system from attacking both normal tissues (self) and malignant cells; immunotherapy can take advantage of this process by inhibiting the checkpoints and allowing the immune system to aggressively attack cancer cells.

Breast Cancer

Introduction

Breast cancer is the most common type of cancer in women in the United States, excluding skin cancers. In 2019, there were approximately 268,600 new invasive breast cancer cases and 48,100 in situ cases diagnosed. The lifetime risk of developing invasive breast cancer is 12.4% (about 1 in 8) for women in the United States. There were an estimated 40,610 deaths from breast cancer in the United States in 2017–the second leading cause of cancer death in women. The lifetime risk of dying from breast cancer for women in the United States is 2.76%. Breast cancer is rare in men.

Epidemiology and Risk Factors

Breast cancer incidence increases with age. The median age of diagnosis in women is 61 years. Incidence rates are highest in non-Hispanic White and Black women. Other risk factors for breast cancer are listed in **Table 2**.

Patients with deleterious *BRCA1* or *BRCA2* gene mutations have a 50% to 85% lifetime risk of breast cancer. Patients who received chest wall irradiation between ages 10 and 30 years for treatment of Hodgkin lymphoma have a 30% to 50% risk of breast cancer. Atypical breast lesions, such as atypical hyperplasia or lobular carcinoma in situ, result in a cumulative 30-year breast cancer risk of up to 35%.

Patients with possible hereditary breast cancer syndromes should be referred to a genetic counselor for assessment and possible genetic testing. The U.S. Preventive Services Task Force recommends assessment of women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or those who have a family history of *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Validated tools are available at https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. The National Comprehensive Cancer Network criteria for genetic testing are outlined in **Table 3**.

KEY POINTS

- Breast cancer incidence increases with age, with the highest incidence in non-Hispanic White women and second highest in Black women.
- Women with possible hereditary breast cancer syndromes should be referred to a genetic counselor for possible genetic testing for breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*.

Chemoprevention and Other Risk Reduction Strategies

Breast cancer screening for average-risk women is discussed in General Internal Medicine 2. The American

TABLE 2. Breast Cancer Risk Factors

Breast Cancer Risk Factor Category	Breast Cancer Risk Factors	Increase in Breast Cancer Risk or Lifetime Breast Cancer Risk
Reproductive factors	Early menarche, late menopause, first full-term pregnancy after age 30 years, nulliparity	RR, 1.2-3.5
Lifestyle	Obesity (BMI ≥30), lack of regular exercise, alcohol intake	RR, 1.2-1.6[a,b,c]
Treatment related: radiation	Prior chest wall irradiation in patients younger than 30 years (e.g., mantle irradiation for Hodgkin lymphoma)	RR, 5.0[d]
Treatment related: HRT	Combination estrogen and progesterone HRT after menopause	RR, 1.2-1.4[a]
Breast density[e]	Increased breast density	Risk increases with each category of breast density; for ≥75% density, RR is 4.7 compared with <10% density[f]
Atypical breast lesions	Atypical ductal or lobular hyperplasia, LCIS	RR, 3.8-5.3[g] RR, 5.4-8.0[h]
Family history of breast cancer and familial breast cancer syndromes	*BRCA1/2* mutation represents the most common familial breast cancer syndrome (5%-10% of all breast cancer tumors); others are rare	RR, 3.0-7.0

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; RR = relative risk.

[a] Data from Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001 Jan 25;344 (4):276-85. Erratum in: N Engl J Med. 2001 Jun 7;344(23):1804. [PMID: 11172156]

[b] Data from Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. [PMID: 21113759]

[c] Data from Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013 Feb;24(2):301-8. [PMID: 22910838] and Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998 Feb 18;279(7):535-40. [PMID: 9480365]

[d] Data from Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

[e] Breast density refers to the amount of radiologically dense breast tissue appearing on a mammogram.

[f] Data from Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. [PMID: 17229950]

[g] Data from Degnim AC, Cisscher DW, Berman HK, et al. Stratifications of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007 Jul 1;25(19):2671-77. [PMID: 17563394] and Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997 May;6(5):297-301. [PMID: 9149887]

[h] Data from Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long-term risk of breast cancer and relation to other factors. Cancer. 1996 Sep 1;78(5):1024-34. [PMID: 8780540]

TABLE 3. Highlights of NCCN[a] Recommendations for Breast and Ovarian Cancer Syndrome Genetic Testing

Individuals with a Personal History of Breast or Ovarian Cancer
Breast cancer diagnosed at or before age 45 years
Breast cancer diagnosed at age 46-50 years with one or more relatives[b] with breast, ovarian, prostate, or pancreatic cancer at any age
Women with two primary breast cancers, with the first diagnosed at or before age 50 years
Breast cancer diagnosed at any age with one or more relatives[b] diagnosed with ovarian cancer, breast cancer diagnosed at or before age 50 years, male breast cancer, metastatic prostate cancer, pancreatic cancer
Triple-negative breast cancer[c] diagnosed at or before age 60 years
Breast cancer in women of Ashkenazi (Eastern European) Jewish ancestry
Men with breast cancer diagnosed at any age
Ovarian cancer diagnosed at any age
Individuals without a Personal History of Breast or Ovarian Cancer
Family history of a known deleterious *BRCA1/2* mutation
BRCA1/2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type
Any individual with one or more first- or second-degree relatives meeting the above criteria

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; NCCN = National Comprehensive Cancer Network; USPSTF = U.S. Preventive Services Task Force.

[a] Full testing guidelines can be accessed at https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

[b] First-, second-, or third-degree relatives on the same side of the family.

[c] Negative for estrogen and progesterone receptors and *HER2* amplification.

TABLE 4. American Cancer Society Recommendations for MRI Breast Cancer Screening

Women with *BRCA1/2* mutations
Women who are a first-degree relative of a *BRCA1/2* carrier but are untested[a]
Women with a strong family history of breast cancer with a lifetime breast cancer risk of ≥20% to 25% as calculated by models[b] largely dependent on family history
Women who had radiation to the chest wall between ages 10 and 30 years (e.g., mantle radiation therapy for Hodgkin lymphoma)
Women with a history of other rare familial breast cancer syndromes

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes.

[a] Testing for the *BRCA1* or *BRCA2* mutation that is present in the family is strongly recommended, but some patients decide to defer testing. In this situation when their carrier status is unknown, breast MRI screening is recommended. If they are later tested and do not carry the mutation, MRI screening should be stopped.

[b] Models that can be used to estimate lifetime risk of breast cancer to determine if MRI screening is appropriate (please note that the Gail Model is not recommended for this use):

- BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- Claus model: Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first-degree family history of ovarian cancer. Breast Cancer Res Treat. 1993 Nov;28(2):115-20. [PMID: 8173064]
- Tyrer-Cuzik (also called IBIS Breast Cancer Risk Evaluation Tool): www.ems-trials.org/riskevaluator/

Cancer Society recommends screening certain women at high risk using annual mammography and breast MRI (**Table 4**).

The National Comprehensive Cancer Network recommends that women with a 5-year risk of breast cancer of 1.67% or greater are candidates for breast cancer chemoprevention with antiestrogens. A recommended tool for estimating 5-year and lifetime risks of breast cancer is the Gail Model Risk Assessment Tool (https://www.cancer.gov/bcrisktool/). All patients with atypical hyperplasia or lobular carcinoma in situ are candidates for chemoprophylaxis. Contrary to the National Comprehensive Cancer Network, the U.S. Preventive Services Task Force advises against using any hard cut-off point for defining increased risk but suggests focusing instead on each woman's values and priorities in weighing the reduced risk of breast cancer with increased likelihood of adverse effects.

Tamoxifen and raloxifene are selective estrogen receptor modifiers that block estrogen uptake in breast tissue. Exemestane and anastrozole are aromatase inhibitors that prevent the conversion of androgens into estrogens. These agents proportionally decrease the risk of breast cancer by 28% to 65% and are given for 5 years. **Table 5** summarizes these chemoprophylaxis options.

For women with *BRCA1* or *BRCA2* mutations, breast cancer screening with breast MRI should start at age 25 years and with mammography added at age 30 years. Prophylactic bilateral mastectomies for *BRCA1* or *BRCA2* mutation carriers decrease the risk of breast cancer by greater than 90%, whereas prophylactic bilateral salpingo-oophorectomy decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and all-cause mortality to age 70 years by 77%. Premenopausal prophylactic bilateral salpingo-oophorectomy also decreases the risk of breast cancer by 50% and is recommended after completion of childbearing.

KEY POINTS

- Women at high risk for breast cancer should be screened with annual mammography and breast MRI; this includes women with gene mutations who have a high risk of breast cancer including *BRCA1* or *BRCA2*, women with a strong family history of breast cancer, and those with a history of chest irradiation at a young age.
- Women with an elevated 5-year risk of breast cancer or with lobular carcinoma in situ or atypical hyperplasia should be considered for breast cancer chemoprophylaxis.
- Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy.

Staging and Prognosis of Early-Stage Breast Cancer

Breast cancer staging and prognosis are presented in **Table 6**. In addition to the excellent prognosis for patients with small tumors with neither lymph node involvement nor distant metastases, the presence of hormone receptors and absence of human epidermal growth factor 2 (*HER2*) overexpression also favorably affect prognosis. Hormone receptor positivity also predicts risk reduction from antiestrogen therapy. Monoclonal antibodies such as trastuzumab that block *HER2* receptors are effective therapies and have markedly improved the prognosis for those with *HER2*-positive breast cancer.

For asymptomatic patients with newly diagnosed stage 0 to II (early-stage) breast cancer, current guidelines recommend against using imaging studies such as PET, CT, bone scan, or measuring serum markers such as CA15-3 or CA27-29, for staging, as the incidence of asymptomatic metastases is low. However, imaging studies for staging are recommended in patients with stage III disease or in those with earlier-stage disease who have signs or symptoms suggestive of metastatic disease.

TABLE 5. Primary Chemoprevention for Breast Cancer

Considerations	Tamoxifen	Raloxifene	Exemestane	Anastrozole
Mechanism of action	SERM	SERM	Aromatase inhibitor	Aromatase inhibitor
Breast cancer risk reduction	43% at 7 years[a] 28% at 10 years[b]	As effective as tamoxifen at reducing the risk of invasive cancers, but less effective at reducing noninvasive cancers[c]	65% at 3 years[d]	53% at 5 years[e]
Important toxicities	Vasomotor symptoms, cataracts, vascular events (stroke, TIA, VTE), and endometrial cancer and uterine sarcoma in postmenopausal women	Vasomotor symptoms, cataracts, vascular events (25% lower risk of vascular events than with tamoxifen)	Vasomotor symptoms, vaginal dryness, sexual dysfunction, arthralgia, headaches, and insomnia	Vasomotor symptoms, vaginal dryness, sexual dysfunction, arthralgia, carpal tunnel syndrome, dry eyes, and hypertension
Indicated for use in premenopausal women	Yes	Not studied; should not be used unless part of a clinical trial	Not effective in premenopausal women	Not effective in premenopausal women
Other	Contraindicated in women with prior thromboembolic events; 32% reduction in osteoporotic fractures[a]	Contraindicated in women with prior thromboembolic events	At 3-year follow-up, no increase in osteoporosis, fractures, endometrial cancer, vascular events, or cardiac disease	At 5-year follow-up, no increase in thromboembolic events, fractures, cerebrovascular events, or myocardial infarction

SERM = selective estrogen receptor modulator; TIA = transient ischemic attack; VTE = venous thromboembolism.

[a] Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005 Nov 16;97(22):1652-62. [PMID: 16288118]

[b] Cuzick J, Sestak I, Cawthorn S, et al; IBIS-I Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015 Jan;16(1):67-75. [PMID: 25497694]

[c] Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006 Jun 21;295(23):2727-41. Erratum in: JAMA. 2006 Dec 27;296(24):2926. [PMID: 16754727]

[d] Goss PE, Ingle JN, Alés-Martínez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. [PMID: 21639806]

[e] Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014 Mar 22;383(9922):1041-48. Erratum in: Lancet. 2014 Mar 22;383(9922):1040. [PMID: 24333009]

TABLE 6. Staging and Prognosis of Invasive Breast Cancer

Stage	Definition	5-Year Relative Survival[a] Rates
0	Ductal carcinoma in situ (negative lymph nodes)	100%
Localized	IA: Tumor ≤2 cm and negative lymph nodes	98.9%
	IB: Tumor ≤2 cm and 1 to 3 micrometastatic positive lymph nodes (0.2-2 mm)	
Regional	IIA: Tumor ≤2 cm with 1 to 3 positive lymph nodes (>2 mm) *OR*	85.7%
	Tumor 2-5 cm with negative lymph nodes	
	IIB: Tumor 2-5 cm with 1 to 3 positive lymph nodes *OR*	
	Tumor >5 cm with negative lymph nodes	
	IIIA: Tumor ≤5 cm with 4 to 9 positive lymph nodes *OR*	
	Tumor >5 cm with 1 to 9 positive lymph nodes	
	IIIB: Tumors with skin or chest wall involvement with 0 to 9 positive lymph nodes	
	IIIC: Tumors with 10 or more positive lymph nodes	
Distant	Distant metastatic disease	28.1%

[a] Relative survival is the ratio of the proportion of observed survivors in a cohort of patients with cancer to the proportion of expected survivors in a comparable set of cancer-free individuals.

Data from Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020. Accessed January 1, 2021.

Breast cancer survival has improved dramatically. American Cancer Society data from 1989 to 2017 show a 40% decrease in deaths from breast cancer. The 5-year relative survival for all invasive breast cancer stages in patients diagnosed from 2010 to 2016 is 91.4%.

KEY POINTS

- Clinical features associated with a more favorable prognosis of early-stage breast cancer include hormone receptor–positive cancer, small tumor size, low tumor grade, negative lymph nodes, and the absence of *HER2* overexpression.
- HVC Imaging studies such as PET, CT, or bone scan for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.

Primary Breast Cancer Therapy

Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), classified as stage 0 breast cancer, is a noninvasive breast cancer that usually presents as calcifications on mammography (**Figure 1**). Its incidence has increased greatly, from 3% of breast cancers before the era of mammographic screening to 20% to 25% of breast cancers today. Patients with DCIS infrequently present with a palpable mass or with Paget disease of the breast (see Invasive Breast Cancer).

Because half of local recurrences of DCIS are invasive cancers, the goal of treatment is to eradicate the area of DCIS and decrease the risks of local recurrence and deaths from breast cancer. Surgical treatment involves either lumpectomy, often followed by breast irradiation, or mastectomy. Irradiation may be omitted in some cases of estrogen receptor–positive DCIS. Mastectomy is recommended if the DCIS is more extensive and cannot be fully removed by a wide excision. Post-lumpectomy irradiation and mastectomy improve disease-free survival but not breast cancer–specific mortality.

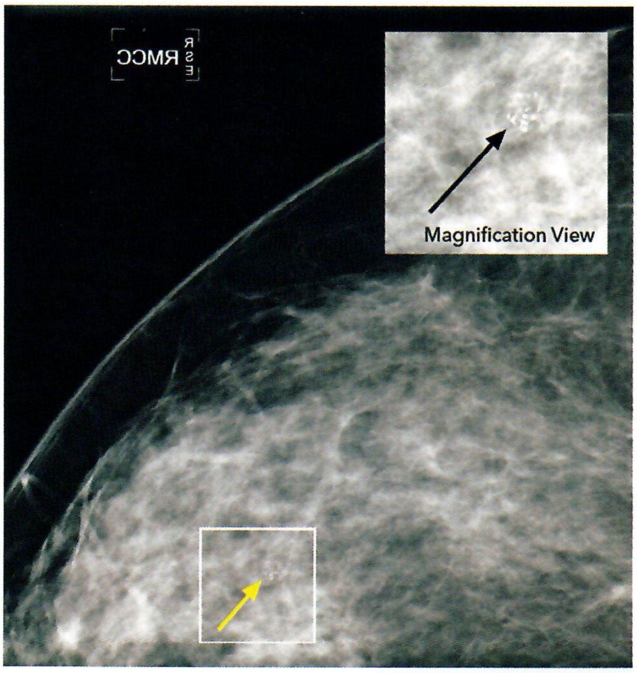


FIGURE 1. Ductal carcinoma in situ presenting as calcifications on mammography.

In women with estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors decrease the risks of local recurrence and contralateral breast cancers. Tamoxifen is the appropriate treatment in premenopausal women. For postmenopausal women, both tamoxifen and anastrozole are effective options; antiestrogen treatment of DCIS does not increase survival. Adjuvant endocrine therapy is not indicated.

Patients with DCIS should undergo annual mammography starting 6 to 12 months after radiation therapy, if given, and follow-up visits every 6 to 12 months for 5 years after diagnosis.

KEY POINTS

- Mastectomy or post-lumpectomy irradiation decreases the risk for local recurrence in women with ductal carcinoma in situ but does not improve overall 10-year survival.
- In estrogen receptor–positive ductal carcinoma in situ, tamoxifen and aromatase inhibitors further decrease the risks of local recurrence and contralateral breast cancer but do not improve overall survival.

Invasive Breast Cancer

Most early-stage invasive breast cancers are treated with initial excision followed by irradiation and adjuvant systemic therapy. There are two surgical options for invasive breast cancer. Breast conservation therapy involves wide excision followed by breast irradiation and is typically used in patients with cancers 5 cm or less in size, without skin involvement, and with clear margins after excision. Mastectomy is recommended for cancers that are too large to allow a lumpectomy with an acceptable cosmetic outcome, cancers with skin involvement, and inflammatory breast cancers. Mastectomy may also be chosen in situations when irradiation is contraindicated, or in women with *BRCA1* or *BRCA2* mutations or strong family histories of breast cancer in which there is a high risk of new breast cancers. For some patients with large tumors, neoadjuvant chemotherapy or endocrine therapy can be given before surgery to shrink the tumor to facilitate breast conservation.

A sentinel node biopsy is done at the time of breast surgery in patients with clinically negative axillary lymph nodes. In patients undergoing breast conservation surgery who will receive chemotherapy or antiestrogen therapy as well as whole breast irradiation, axillary dissection is not required if no more than two sentinel nodes are involved. For patients with clinically involved axillary nodes or three or more positive sentinel nodes, an axillary dissection is recommended. An axillary dissection is also performed if the sentinel nodes are not identified, which occurs in 5% of cases. The sentinel node procedure has a lower risk of lymphedema, sensory loss, and shoulder abduction defects than axillary dissection.

Primary breast irradiation usually consists of irradiation to the whole breast, although partial breast irradiation is an option in some patients. Postmastectomy irradiation is generally recommended for tumors larger than 5 cm, positive margins or skin involvement, inflammatory breast cancers, or four or more positive axillary nodes and often for women with one to three positive axillary nodes. Postmastectomy irradiation decreases both the risk of local recurrence and the risk of distant metastases and increases overall survival.

For women older than age 70 years with cancers less than 2 cm in size, no clinically involved lymph nodes, and estrogen receptor–positive breast cancer, wide excision followed by antiestrogen therapy alone is an acceptable treatment option. Whole breast irradiation in this situation decreases the risk of local recurrence from 9% to 2% at 12 years but has no impact on the risk of distant metastases, breast cancer–specific survival, or overall survival.

Paget disease of the breast is an uncommon manifestation of breast cancer, characterized by a scaly or red rash or ulceration occurring on the nipple and spreading to the areola. It may have a similar appearance to atopic or contact dermatitis. Paget disease usually occurs in association with an underlying ductal breast cancer and is diagnosed through a skin biopsy or scrape cytology, which shows involvement of the epidermis by neoplastic cells. Upon diagnosis, patients should undergo diagnostic breast imaging and, if no abnormalities are detected, breast MRI should be considered to evaluate for occult disease. Prognosis and management are determined by the standard features of an in situ or invasive carcinoma. Depending on the extent of disease within the breast, breast-conserving therapy may be appropriate, although all patients require nipple-areolar resection.

KEY POINTS

- Breast-conserving therapy is effective for many women with small (<5 cm) tumors, no skin involvement, and clear margins after resection; breast irradiation is recommended subsequently in most patients.
- Postmastectomy irradiation is recommended for cancers greater than 5 cm in size, positive margins or skin involvement, inflammatory breast cancers, and most patients with positive axillary lymph nodes.

Adjuvant Systemic Therapy for Nonmetastatic Breast Cancer

Patients with stage I to III (potentially curable) breast cancer receive adjuvant systemic therapy to eradicate occult microscopic foci of breast cancer and decrease the risk of local and distant recurrence. The type of adjuvant therapy used depends on the biology and stage of the breast cancer.

Adjuvant Endocrine Therapy

Approximately 75% of breast cancers are hormone receptor–positive (positive for the estrogen receptor, progesterone receptor, or both). Patients with hormone receptor–positive breast cancers should receive adjuvant antiestrogen therapy for at least 5 years. The Early Breast Cancer Trialists Collaborative Group meta-analysis of adjuvant tamoxifen showed a 39% proportional reduction in breast cancer recurrence at 15 years and a 30% proportional reduction in breast cancer mortality. In postmenopausal women, aromatase inhibitors are superior to tamoxifen, with a further 29% proportional decrease in breast cancer recurrence. Both tamoxifen and aromatase inhibitors also decrease the risk of contralateral breast cancer.

Tamoxifen is a selective estrogen receptor modulator that blocks estrogen uptake by breast cancer cells. It is effective in both premenopausal and postmenopausal women. The aromatase inhibitors letrozole, anastrozole, and exemestane have similar efficacy and prevent conversion of adrenal androgens to estrogen but do not inhibit ovarian estrogen production. They are thus not effective in premenopausal women unless ovarian suppression is given concomitantly.

For postmenopausal women, 5 years of an aromatase inhibitor or 2 years of tamoxifen followed by 3 years of an aromatase inhibitor is associated with a significantly lower risk of recurrence and with improved survival in women with higher-grade ductal cancers or lobular cancers. Extended aromatase therapy up to 10 years reduces disease-free survival in patients with high-risk features but does not have an impact on overall survival. Decisions regarding extended aromatase inhibitor therapy should be tailored to patient risk and comorbidities that may affect tolerability, including bone health and history of venous thromboembolic disease.

Endocrine therapy options for premenopausal women with estrogen receptor–positive breast cancer include tamoxifen, ovarian function suppression (OFS) with tamoxifen, or OFS with an aromatase inhibitor. For those with low recurrence risk, tamoxifen alone for 5 years may be appropriate. Extended tamoxifen therapy to 10 years is associated with a reduction in recurrence risk (3.7%) and breast cancer mortality (2.8%). Disease-free survival is improved in premenopausal women with higher-risk cancers with the addition of OFS. Patients treated with OFS had more hot flushes, vaginal dryness, decreased libido, insomnia, depression, arthralgia, hypertension, glucose intolerance, and osteoporosis.

Adverse effects of tamoxifen and aromatase inhibitors are shown in Table 5. Up to one third of women treated with aromatase inhibitors develop aromatase inhibitor–associated symmetric arthralgia, joint stiffness, and bone pain. This musculoskeletal syndrome is managed with NSAIDs or duloxetine, a treatment break and changing to an alternate aromatase inhibitor, or a change to tamoxifen.

KEY POINTS

- Endocrine therapy in women with hormone receptor–positive breast cancer substantially reduces the risk of recurrence and improves overall survival.
- Endocrine therapy options for premenopausal women include tamoxifen, ovarian function suppression (OFS) plus tamoxifen, or OFS plus an aromatase inhibitor; women at low recurrence risk may be treated with tamoxifen alone.
- Five years of an aromatase inhibitor or 2 years of tamoxifen followed by 3 years of an aromatase inhibitor is associated with a significantly lower risk of recurrence and with improved survival in postmenopausal women with higher-grade ductal cancers or lobular cancers.
- Extended aromatase inhibitor treatment up to 10 years reduces recurrence risk relative to 5 years in patients with higher-risk cancer but does not improve overall survival.

Adjuvant Chemotherapy

Increasingly, the use of adjuvant chemotherapy for early breast cancer is based more on tumor biology rather than on stage. Hormone receptor–negative and *HER2*-positive cancers are associated with greater recurrence as well as greater risk reduction from chemotherapy. Adjuvant chemotherapy is recommended for women with cancers of these subtypes that are either greater than 5 mm or lymph node positive.

For hormone receptor–positive, *HER2*-negative breast cancers with zero to three positive axillary nodes, the use of multigene assays (e.g., the 21-gene recurrence score assay) that predict the risk of recurrence with antiestrogen therapy alone has significantly decreased the use of adjuvant chemotherapy. Women with node-negative breast cancer and low and intermediate recurrence scores have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy. Similar findings have been seen for women with one to three positive nodes with low and intermediate risk recurrence scores, but these conclusions remain controversial.

Clinicopathologic factors that suggest benefit from adjuvant chemotherapy include high tumor grade, extensive lymphatic invasion, larger tumor size, skin or chest wall involvement, and involvement of more than four axillary nodes.

Women with hormone receptor–negative, *HER2*-negative cancers (triple-negative breast cancer) have a 50% proportional reduction in the risk of recurrence and of breast cancer mortality with adjuvant chemotherapy. Adjuvant chemotherapy is recommended for patients with triple-negative cancers larger than 5 mm in size or with positive lymph nodes.

When adjuvant chemotherapy is given for high-risk hormone receptor–positive cancers or triple-negative cancers, typically two or three agents are given for four to eight cycles. The most common chemotherapies used for adjuvant treatment are anthracyclines (doxorubicin or epirubicin), cyclophosphamide, and the taxanes (paclitaxel or docetaxel).

Adjuvant chemotherapy combined with *HER2*-targeted treatment such as the monoclonal antibody trastuzumab or the combination of trastuzumab and pertuzumab is recommended for *HER2*-positive cancers that are greater than 5 mm in size, node positive, or both. The addition of trastuzumab to chemotherapy decreases the risk of cancer recurrence by 53% and the risk of death by 34%. Trastuzumab is generally given for 12 months in total. For patients with node-negative *HER2*-positive breast cancers smaller than 3 cm in size, weekly paclitaxel and trastuzumab is a well-tolerated regimen with a 7-year recurrence-free survival rate of 97.5%. Neoadjuvant chemotherapy is generally recommended for patients with larger or node-positive tumors and involves multiple chemotherapy agents along with trastuzumab and pertuzumab. Patients with no residual disease at surgery have an excellent prognosis. Patients with residual disease following preoperative chemotherapy have a greater recurrence risk, and subsequent use of ado-trastuzumab-emtansine (an antibody-drug conjugate that links trastuzumab to the microtubule inhibitor emtansine) reduces recurrence risk by 50% relative to trastuzumab. The main toxicities of trastuzumab are infusion reactions such as fever, chills, and cardiomyopathy.

Acute adverse effects of adjuvant chemotherapy include bone marrow suppression, alopecia, allergic reactions, neuropathy, nausea, and premature menopause and infertility in premenopausal women (see Effects of Cancer Therapy and Survivorship). Women of childbearing age who wish to preserve fertility may undergo oocyte or embryo banking before chemotherapy. Serious long-term toxicities include cardiomyopathy, neuropathy, myelodysplasia, and acute myelocytic leukemia. The risk of cardiomyopathy after four cycles of an anthracycline is 1.5%. The risk of acute leukemia after regimens containing an anthracycline or cyclophosphamide is 0.5%.

For women of advanced age with higher-risk early breast cancer, it is important to consider estimated life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy. There is a higher risk of cardiotoxicity in older women.

KEY POINTS

- Patients with hormone receptor–positive, node-negative breast cancer and low or intermediate risk recurrence scores have a favorable prognosis with antiestrogen therapy and do not benefit from chemotherapy.
- Adjuvant chemotherapy is appropriate for patients with triple-negative or *HER2*-positive tumors greater than 5 mm in size or with positive axillary lymph nodes.

Locally Advanced and Inflammatory Breast Cancer

Locally advanced breast cancer includes a subset of clinical stage IIB cancers (T3N0M0), as well as stages IIIA to IIIC cancers. These cancers may have high-risk characteristics such as skin involvement, chest wall involvement, extensive lymph node involvement, or inflammatory changes.

Inflammatory breast cancer represents a small subset of locally advanced breast cancer in which patients present with swelling, thickening, or erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance (**Figure 2**). Patients often present with breast enlargement or swelling, often misdiagnosed as mastitis with subsequent delay in management. A palpable breast mass may be present. The skin changes are due to the obstruction of dermal lymphatic vessels by cancer cells, although biopsy may not always reveal that pathology. One third of patients have distant metastases at diagnosis, and nearly all have lymph node involvement. For this reason, these patients should have routine staging with either CT and bone scan imaging or PET scan, even in the absence of metastatic disease symptoms.

Locally advanced cancers are usually treated initially with neoadjuvant chemotherapy, followed by surgery, and then irradiation. In some postmenopausal women, neoadjuvant antiestrogen therapy can be used instead of chemotherapy. Patients with inflammatory breast cancer require mastectomy, but in other patients, neoadjuvant therapy may decrease the size of the primary breast cancer to allow for breast-conserving lumpectomy. Patients will generally receive radiation therapy afterward. The amount of residual cancer after neoadjuvant chemotherapy has prognostic significance, particularly in triple-negative or hormone-negative, *HER2*-positive cancers. Patients with complete pathologic responses have the lowest risk of recurrence, whereas those with residual disease may benefit from treatment intensification with additional chemotherapy.

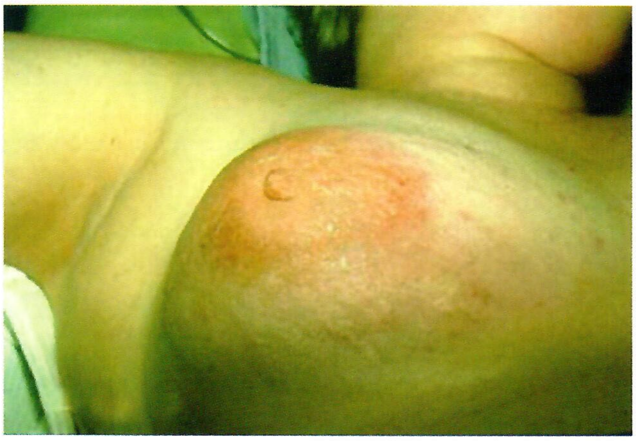


FIGURE 2. Inflammatory breast cancer often has a characteristic "p'eau d'orange" (orange peel) appearance of the skin, due to tumor emboli in the dermal lymphatics. Erythema is also often present.

KEY POINTS

- Inflammatory breast cancer, characterized by swelling, thickening, and erythema of the skin overlying the breast, may be mistaken for infectious mastitis and delay evaluation and treatment.
- Locally advanced cancers are usually treated with neoadjuvant chemotherapy or endocrine therapy, surgery, and irradiation.

Breast Cancer Follow-up and Survivorship

There are nearly 3 million women alive in the United States with a previous or current diagnosis of breast cancer. Following early active therapy (surgery, chemotherapy, and irradiation), patients are monitored for recurrence, second primary cancers, and physical and psychosocial long-term effects of breast cancer and treatment. Patients with hormone receptor-positive breast cancer remain on antiestrogen treatment for 5 to 10 years and require management of menopausal symptoms and other toxicities, including bone loss, during that time. Guidelines recommend that patients be evaluated for a detailed cancer-related history and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually.

Patients should have annual mammograms of remaining breast tissue. Screening breast MRIs are needed only if patients meet criteria for screening MRIs (see Chemoprevention and other Risk Reduction Strategies). Patients should not have routine blood tests at follow-up visits or other routine imaging studies, as these are not helpful for diagnosing recurrences earlier. Laboratory and imaging studies other than breast imaging should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.

Patients should be evaluated at each visit for changes in family history of cancers and referred for genetic counseling as appropriate. Patients on tamoxifen should have annual gynecologic examinations and be evaluated by a gynecologist for any abnormal vaginal bleeding. Patients on aromatase inhibitors should have bone density studies every 2 years and should receive osteoporosis treatment, ideally with a bisphosphonate, if their T score is −2.5 or lower.

For patients with breast asymmetry, reconstruction options are often fully covered by insurance. Patients should receive physical therapy for lymphedema or decreased arm mobility after surgery or irradiation to axillary nodes. Menopausal symptoms should be managed with nonhormonal options, such as gabapentin for nocturnal hot flushes. Depression, anxiety, and sexual dysfunction are not uncommon in this population and should be appropriately assessed and managed. For patients taking tamoxifen, it is important to avoid medications with strong CYP2D6 inhibition, such as bupropion or fluoxetine, as these may decrease tamoxifen activation.

KEY POINTS

- After completing treatment for breast cancer, follow-up monitoring should be every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then every year, with annual mammography for all survivors, and breast MRI for those at high risk of recurrence.
- **HVC** Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.
- Patients taking tamoxifen should have yearly gynecologic examinations because of the increased risk of endometrial cancer, and those on an aromatase inhibitor should have bone density studies every other year to assess osteoporosis.

Metastatic Breast Cancer

Approximately 5% of patients with breast cancer present with metastatic disease, and up to 30% with early-stage disease develop metastases. Metastatic breast cancer is not curable, but systemic therapy can improve survival, relieve symptoms, and maintain quality of life. Treatment and prognosis are related to whether visceral metastases are present, the number of sites involved, the interval between initial diagnosis and metastases (intervals of less than 2 years have a poorer prognosis), the patient's performance status, and tumor biology. The median overall survival for patients with metastatic breast cancer is longer for women with hormone receptor–positive cancer or *HER2*-positive cancer, some of whom may have prolonged survival, in part related to more treatment options.

When evaluating a patient with newly diagnosed metastatic breast cancer, the lesion that upstages the patient to the greatest degree should be biopsied. It is also important to biopsy a site of initial metastasis both to confirm the diagnosis and to assess hormone receptor and *HER2* status, as there may be treatment altering discordance in the receptors in the metastatic lesion compared with the primary breast cancer in 10% to 15% of patients.

In postmenopausal women with hormone receptor–positive, *HER2*-negative breast cancer, endocrine-based therapy is usually the initial treatment. In patients with rapidly progressive disease or extensive visceral metastases, initial chemotherapy may be used because of its higher response rate. Aromatase inhibitors are superior to other agents as first-line treatment. Fulvestrant, which inhibits estrogen receptor function, and tamoxifen are other options. Premenopausal women can receive tamoxifen or ovarian suppression combined with either tamoxifen or aromatase inhibitors as initial treatment.

The addition of CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) to aromatase inhibitors as first-line endocrine therapy or to fulvestrant following progression on an aromatase inhibitor improves the response rate and duration of response to hormonal therapy. These drugs have been incorporated into routine care for the majority of women with metastatic estrogen receptor–positive/*HER2*-negative breast cancer.

For patients with *HER2*-positive advanced breast cancer, treatment should include *HER2*-directed therapy such as trastuzumab given with either chemotherapy or antiestrogen therapy, depending on the hormone receptor status of the cancer and disease sites. First-line treatment with dual *HER2*-targeted therapy with trastuzumab and pertuzumab added to the taxane docetaxel has been shown to improve overall survival, with median overall survival of 56 months in a phase III clinical trial. Ado-trastuzumab emtansine is commonly used as a second-line treatment but may be used as first-line therapy following a treatment-free interval of less than 6 months from adjuvant trastuzumab.

Patients with triple-negative breast cancers (TNBC have a higher relapse rate than individuals with hormone receptor–positive cancers; recur earlier, with a peak at 3 years after diagnosis and a very low risk of relapse after 5 years; and have a higher risk of locoregional recurrence and brain and lung metastases. Advanced TNBC has historically been treated with chemotherapy. The addition of atezolizumab, a monoclonal antibody targeting programmed death ligand 1, to nab-paclitaxel improved overall survival (23.1 vs 17.6 months) for patients with programmed death ligand 1–positive metastatic TNBC. TNBC may also be particularly responsive to platinum agents, particularly in *BRCA* mutation carriers. In patients with germline *BRCA1* or *BRCA2* mutations, poly (ADP-ribose) polymerase inhibitors (olaparib, talazoparib) improve progression-free survival relative to single-agent chemotherapy. These agents cause "synthetic lethality" by producing an increase in double-strand DNA breaks that would usually be repaired by the *BRCA* pathway.

Chemotherapy agents used in patients with advanced breast cancer include taxanes, capecitabine, eribulin, gemcitabine, vinorelbine, ixabepilone, and liposomal doxorubicin. Single-agent chemotherapy is usually given, with combination chemotherapy reserved for patients with extensive visceral metastases where a higher response rate is important.

For all subtypes of breast cancer with bone metastases, bone-modifying agents such as zoledronic acid or denosumab are recommended to decrease fractures, pain, and need for irradiation. Palliative irradiation can be used to treat painful bone metastases as well as other sites of tumor-related pain or obstruction. Patients with TNBC and *HER2*-positive cancers have a higher risk of brain metastases, which are treated with surgery, stereotactic irradiation, or whole brain irradiation. Palliative care teams can be helpful for managing symptoms of pain, nausea, anorexia, and fatigue. Throughout the course of advanced breast cancer, discussions with patients about their goals of care should take place, focusing on their values and preferences as they are treated for an incurable illness.

KEY POINTS

- Metastatic breast cancer is not curable, but it can be treated with systemic therapy with the goals of improved survival, symptom palliation, and maintaining quality of life.
- The site of initial metastasis should be biopsied to confirm the diagnosis and to assess hormone receptor and *HER2* status, which can be discordant from the primary breast cancer.

Ovarian Cancer

Epidemiology and Risk Factors

Risk factors for epithelial ovarian cancer include mutations of ovarian cancer susceptibility genes, increasing age, infertility, nulliparity, endometriosis, polycystic ovary syndrome, and cigarette smoking.

The most common ovarian cancer susceptibility genes are *BRCA1*, *BRCA2*, and the mismatch repair (MMR) genes associated with Lynch syndrome. Approximately 10% to 15% of women with ovarian cancer carry a mutation in one of these genes, and all women with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1* and *BRCA2* mutations. In patients with a personal or family history of other Lynch syndrome cancers (e.g., colorectal cancer, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), MMR mutation testing is recommended as well. The cumulative lifetime risk of ovarian cancer is 45% in *BRCA1* carriers and 3% to 12% in the other gene mutation carriers.

KEY POINT

- Genetic testing for *BRCA1* and *BRCA2* mutations should be offered to all women with ovarian cancer.

Risk-Reduction Strategies and Screening

For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing. For *BRCA1* or *BRCA2* carriers, prophylactic bilateral salpingo-oophorectomy decreases the risk of ovarian cancers by greater than 80% and decreases all-cause mortality to age 70 years by 77%. Recommendations for genetic testing for breast and ovarian cancer syndromes are discussed in Breast Cancer.

Ovarian cancer screening with transvaginal ultrasonography or serum CA-125 is not recommended for patients of average risk and has no proven benefit even in women with high-risk genetic mutations.

KEY POINT

- For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing.

Diagnosis

Patients with ovarian cancer usually present at an advanced stage with bloating, abdominal or pelvic pain, constipation, or early satiety. Initial evaluation should include a pelvic examination, general physical examination, serum CA-125 level, complete blood count, liver chemistry tests, and transvaginal ultrasonography. Additional CT or MRI imaging are done as clinically indicated. Patients with a high suspicion of ovarian cancer should be referred to a gynecologic oncologist.

For early ovarian cancer, surgical exploration is recommended for diagnosis because removing the ovarian cancer intact without rupture improves survival. For advanced ovarian cancers with peritoneal masses, ascites, or pleural effusions, fluid cytology or image-guided biopsy can be done, particularly if the disease is not initially resectable and neoadjuvant chemotherapy may be used.

Staging and prognosis are shown in **Table 7**. Early stage, low grade, serous histology, extent of disease after surgical debulking, and young age are associated with improved survival. A total of 31% of patients diagnosed with ovarian cancer survive 10 years, with one third of these long-term survivors having stage III or IV cancer.

Treatment

Surgical staging includes total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, omentectomy, and pelvic and para-aortic lymph node sampling. Surgical debulking, including the resection of metastatic disease, improves prognosis. The volume of residual disease after surgery correlates inversely with survival. Neoadjuvant chemotherapy is recommended for patients with initially unresectable disease to shrink the tumor to facilitate surgical debulking.

Patients with early-stage ovarian cancer who have favorable histology may be treated with surgical resection alone. All other patients should receive adjuvant platinum-taxane chemotherapy. When incorporated into systemic therapy, intraperitoneal chemotherapy has been shown to improve survival in some trials, albeit with more toxicity, in women with stage III disease.

Women with advanced ovarian cancer and *BRCA1* or *BRCA2* mutations who achieve some response to traditional chemotherapy should receive subsequent maintenance therapy with olaparib, a poly (ADP-ribose) polymerase inhibitor.

Second-look laparotomy to assess pathologic response is not beneficial.

TABLE 7. International Federation of Gynecology and Obstetrics Ovarian Cancer Staging, Treatment, and Survival

Stage	Definition	Treatment	5-Year Survival
Stage I disease (favorable)[a]	Cancer in one or both ovaries, not high grade or clear cell, negative peritoneal washings, no rupture	Surgery alone	94% overall survival
Stage I disease (unfavorable); stage II disease	Unfavorable stage I disease: confined to ovaries but with high-grade or clear cell histology, rupture, or positive peritoneal washings Stage II disease: spread beyond ovaries but confined to pelvis	Surgery followed by 3 to 6 cycles of chemotherapy (usually carboplatin and paclitaxel)	Stage I: 85% relative survival[b] Stage II: 70%-78% relative survival
Optimally debulked stage III disease	Spread to abdomen, with residual tumor masses <1 cm after debulking surgery	Surgery followed by IV or IV/IP chemotherapy Maintenance olaparib after first-line chemotherapy	IV chemotherapy: 40% overall survival IV/IP chemotherapy: 50% overall survival (23% decreased risk of death with IP/IV versus IV chemotherapy)
Suboptimally debulked stage III disease or stage IV disease[c]	Stage III (suboptimal) disease: spread to abdomen with residual masses >1 cm after debulking surgery Stage IV disease: spread beyond abdomen	Surgery (usually done even for stage IV disease as it improves survival) and chemotherapy; preoperative (neoadjuvant) chemotherapy given for initially unresectable cancer Maintenance olaparib after first-line chemotherapy	Stage III: 39% relative survival Stage IV: 17% relative survival

IP = intraperitoneal; IV = intravenous.

[a] Careful staging is critical: almost one third of patients with apparent early disease will have more advanced disease when thorough staging is completed.

[b] Relative survival is the ratio of the proportion of observed survivors in a cohort of patients with cancer to the proportion of expected survivors in a comparable set of cancer-free individuals.

[c] According to recent guidelines by the American Society of Clinical Oncology and the Society of Gynecologic Oncology, patients with stage IIIC or IV ovarian cancer who are at high perioperative risk or who have a low likelihood of optimal tumor debulking should receive neoadjuvant chemotherapy followed by reevaluation for cytoreductive surgery.

KEY POINTS

- Patients with stage I ovarian cancer with favorable histology may be treated with surgery alone; all other patients should receive platinum-taxane chemotherapy.
- HVC Second-look laparotomy to assess pathologic response following chemotherapy of ovarian cancer should not be performed.

Monitoring and Follow-up

Posttreatment surveillance consists of physical and pelvic examinations every 3 to 6 months for 5 years, then annually. Surveillance of CA-125 levels may indicate early tumor progression but does not have an impact on survival. Other testing is recommended only to evaluate symptoms or findings suggesting recurrence.

Management of Recurrent Ovarian Cancer

Despite optimal treatment, 80% to 85% of women with stage III or IV ovarian cancer will relapse. Patients who relapse 6 months or more after initial chemotherapy are considered to have platinum-sensitive disease, have a better prognosis, and are usually treated with platinum-containing combination chemotherapy. Adding the angiogenesis inhibitor bevacizumab to combination chemotherapy improves disease-free survival but increases the risk of serious gastrointestinal toxicities. For patients with platinum-resistant disease, various single agents can be used.

KEY POINT

- Patients who relapse more than 6 months after discontinuing platinum-based chemotherapy for ovarian cancer are considered to have platinum-sensitive disease and should be treated with platinum-based combination chemotherapy.

Cervical Cancer

Epidemiology and Risk Factors

In the United States, approximately 13,000 new patients are diagnosed with invasive cervical cancer per year, and about 4200 deaths are reported. The mean age of diagnosis in the

TABLE 8. International Federation of Gynecology and Obstetrics Cervical Cancer Staging and Treatment

Stage	Treatment
I: Carcinoma is strictly confined to the cervix IA: Microscopic disease only, up to 5 mm in depth IB: Clinically visible disease, or microscopic disease >5 mm	IA and IB: Modified radical (for lesions <2 cm) or radical hysterectomy with pelvic lymph node dissection is preferred; if poor functional status, irradiation can be used instead. If treated with surgery, adjuvant irradiation or chemoradiation is added if indicated based on final pathology. Fertility preservation surgery is an option for cancers ≤2 cm with no lymph node metastases. IA: Simple hysterectomy, cone biopsy (conization), or removal of cervix (trachelectomy) are options.
IIA and IIB: Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or lower third of the vagina. IIB has parametrial invasion.	IIA: Same as for stage I IIB: Same as for stage III
III: The tumor extends to the pelvic wall, involves the lower third of the vagina, causes hydronephrosis or nonfunctioning kidney, and/or involves the pelvic or para-aortic lymph nodes.	III: Irradiation with concurrent platinum-based chemotherapy
IV: The carcinoma extends beyond the true pelvis or involves the mucosa of the bladder or rectum. IVA: Spread to adjacent organs IVB: Distant metastases	IVA: Same as for stage III IVB: Palliative cisplatin-based chemotherapy, with irradiation for local symptoms, such as bleeding or pain. Pembrolizumab is approved for second-line treatment in patients with programmed death ligand 1–positive tumors.

United States is 48 years. During the last 30 years, cervical cancer incidence and deaths in developed countries have decreased by more than 50%, primarily because of screening and preventive treatment. It remains the second most common cause of mortality from cancer in women worldwide. More than 85% of deaths are in less developed countries.

Human papillomavirus (HPV) is the causative agent in most patients and can be detected in 99.7% of cervical cancers. Risk factors include earlier onset of sexual activity and having several partners. Immunosuppression, including HIV infection, low socioeconomic status, smoking, and oral contraceptive use are additional risk factors. Squamous cell carcinoma is the histologic type in 69% of cervical cancers, with adenocarcinoma accounting for 25%. HPV vaccination markedly decreases the incidence of cervical dysplasia and cervical cancer. Cervical cancer screening and HPV vaccination are covered in General Internal Medicine 2.

KEY POINT

- Human papillomavirus is the causative agent in most patients with cervical cancer, and vaccination significantly reduces the risk.

Diagnosis, Staging, and Treatment

Patients with early cervical cancer are frequently asymptomatic. The most common symptoms are abnormal or heavy vaginal bleeding or vaginal discharge. Pelvic or back pain and bowel or bladder symptoms are symptoms of advanced disease. Diagnosis is made by direct biopsy of a visible lesion, colposcopy, or cone biopsy (conization). Current guidelines for staging studies recommend a complete blood count, liver chemistry tests, kidney function studies, and imaging studies for moderate- and high-risk stage cancers. HIV testing should be considered. Cervical cancer staging and treatment are described in **Table 8**. For patients with tumors 2 cm in size or smaller that are confined to the cervix and with no lymph node involvement, fertility-sparing surgeries such as conization (only for stage IA) or radical trachelectomy, in which the cervix and upper vagina are removed but the uterine corpus is preserved, are options.

KEY POINTS

- Early cervical cancer is frequently asymptomatic, but the most common symptoms are abnormal or heavy vaginal bleeding or vaginal discharge; advanced cervical cancer symptoms include pelvic or back pain and bowel or bladder symptoms.
- Select patients with cervical cancer confined to the cervix can be treated with surgery that preserves fertility.
- Patients with bulky or locally advanced cervical cancer are treated with cisplatin-based chemotherapy and radiation instead of surgery.

Prognosis and Surveillance

The 5-year relative survival for all stages of cervical cancer is 67.5%. The anatomic stage is the most important predictor of prognosis. Ninety percent of patients with localized disease survive 5 years. The 5-year survival rate drops to 58% for patients with regional disease and 17% for patients with disease extending outside of the true pelvis or involving the bladder or rectum.

Surveillance is recommended to monitor for recurrences that are potentially curable. Guidelines recommend a history and physical examination every 3 to 6 months for 2 years, every 6 to 12 months during years 3 to 5, and then annually based on the risk of recurrence. Annual vaginal cytology, cervical cytology, or both is recommended. Imaging and laboratory studies are recommended only if indicated based on symptoms or findings on examination that are suspicious for recurrence.

KEY POINT

HVC
- Annual cervical or vaginal cytology should be done on all cervical cancer survivors; additional surveillance imaging and laboratory studies for cervical cancer survivors are recommended only if there are signs or symptoms suggestive of recurrence.

Gastroenterological Malignancies

Colorectal Cancer

Colorectal cancer (CRC), the fourth most common cancer and second leading cause of cancer death in North America, is largely preventable through screening. Current guidelines recommend routine screening to begin at age 50 years, although the percentage of cases diagnosed below the age of 50 has increased from 10% to 12% over the past decade. CRC screening of average-risk patients is discussed in General Internal Medicine 2. Most colon cancers are adenocarcinomas that begin in the inner lining and progress to involve or spread beyond the full thickness of the bowel wall, to regional lymph nodes, and subsequently to distant organ metastases. Epidemiology, pathophysiology, risk factors, screening, and clinical manifestations will be discussed in Gastroenterology and Hepatology.

Tumors on the midgut-derived right side of the large intestine (cecum, ascending colon, and proximal two thirds of transverse colon) have a markedly different biology, including a substantially worse prognosis, from those rising on the hindgut-derived left side (distal third of the transverse colon, descending colon, sigmoid colon, and rectum). Left-sided tumors are more likely to cause a change in bowel habits. Cancers in the proximal colon rarely cause obstructive symptoms due to the wider lumen and liquid nature of the fecal contents. Patients with right-sided tumors are more likely to present with iron-deficiency anemia due to occult, chronic blood loss. Patients with colon cancer at any location may also present with hematochezia, pain, or acute clinical signs from obstruction, or in rare cases, perforation.

Approximately 15% of CRCs lack one or more mismatch repair enzymes and are known as deficient mismatch repair (dMMR) CRC, manifesting as increased microsatellite instability (MSI) in the cancer cell's DNA and resulting in a condition of hypermutability; the terms *dMMR* and *MSI* are essentially synonymous. All CRCs should be screened for dMMR or MSI. Approximately 20% of patients with dMMR tumors will have a germline mismatch repair deficiency, known as Lynch syndrome, which is discussed in Gastroenterology and Hepatology. Lynch syndrome is autosomal dominant, and patients and family members should be offered formal genetic counseling and more intense cancer surveillance. Mismatch repair status of the tumor can affect treatment choices in patients with stage II or stage IV cancer as discussed in the information to follow.

KEY POINTS

- Tumors arising on the right side of the large intestine have a different biology and substantially worse prognosis than tumors on the left side.
- All colorectal cancers should be screened for mismatch repair enzyme deficiency or microsatellite instability; patients whose tumors test positive should be screened for germline mismatch repair deficiency (Lynch syndrome).

Staging

TNM cancer staging is the first step in treatment planning (**Table 9**). Evaluation includes obtaining carcinoembryonic antigen (CEA) levels in addition to routine laboratory studies; a full colonoscopy (if possible); and contrast-enhanced CT scans of the chest, abdomen, and pelvis. Patients with rectal cancers also require a rectal MRI, which provides greater precision in assessing tumor penetration and lymph node involvement. PET scans do not provide greater accuracy in staging and should not be used unless contrast-enhanced CT scans are contraindicated.

Treatment

Rectal Cancer

Rectal cancers that do not penetrate the full thickness of the bowel wall and do not involve regional lymph nodes are stage I and are treated with surgical resection. Small stage I tumors

TABLE 9. Staging of Colorectal Cancer

Stage	Description	Approximate 5-Year Disease-Free Survival
I	Tumor does not invade the full thickness of bowel wall (T1, T2); lymph nodes not involved (N0)	90%-95%
II	Tumor invades full thickness of the bowel and may invade into pericolonic or perirectal fat (T3, T4); lymph nodes not involved (N0)	70%-85%
III	One or more lymph nodes involved with cancer (N1, N2); any T stage	25%-70%
IV	Metastatic tumor spread to any distant site or peritoneal metastases (M1); any T stage; any N stage	0%-10%

may be resected by a transanal approach, decreasing postoperative morbidity. Unless more extensive disease is found during surgery, no further treatment is warranted.

Full-thickness tumors (stage II) and/or those with involved lymph nodes (stage III) routinely require irradiation, chemotherapy, and surgery. Evidence is insufficient to define an optimal sequencing of the three treatment modalities, although total neoadjuvant therapy (TNT), in which all planned chemotherapy and irradiation is given before surgery, is becoming a more widespread practice. If a complete clinical response to TNT is achieved, nonoperative management with close surveillance may be considered. Attempts are made to preserve anal sphincter function, but if a distal rectal cancer is not fully eradicated by TNT, an abdominal-perineal resection with resultant permanent colostomy is required. Surgery for tumors of the mid rectum and above rarely require a permanent colostomy.

Capecitabine, an oral prodrug that is converted into 5-fluorouracil (5-FU), or, less commonly, intravenous 5-FU, is given concurrently with radiation therapy. Both drugs may be associated with erythema of the palms and soles that may progress to blistering (hand-foot syndrome). Mucositis, diarrhea, and neutropenia may also occur. Leucovorin, 5-FU, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) regimens are typically used for the chemotherapy-only portion of the treatment. Oxaliplatin often causes a peripheral neuropathy, which may not resolve fully.

Following therapy, patients with rectal cancer should be evaluated at approximately 6-month intervals for up to 5 years with a history, physical examination, and serum CEA level assessment. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are typically obtained annually for 5 years.

Colon Cancer

Nonmetastatic colon cancers are initially treated with surgical resection. Pathologic evaluation then determines further treatment.

Patients with microsatellite stable stage II cancer lacking high-risk features, such as poorly differentiated histology, T4 primary tumor, lymphovascular invasion, inadequate lymph node sampling (less than 12), elevated postoperative CEA level, or perforation or obstruction, are at low risk for recurrence and are unlikely to benefit from adjuvant treatment. Patients with one or more of these risk factors may be considered for adjuvant 5-FU or capecitabine. Data are equivocal on the use of FOLFOX or CAPOX.

All patients with stage III (node-positive) colon cancer should receive FOLFOX or CAPOX postoperatively. In those with favorable characteristics (T1-3, N1), 3 months of treatment is noninferior to 6. Patients with T4 and/or N2 disease (four or more positive nodes) are typically treated for 6 months.

Postoperative surveillance after curative resection is used to identify oligometastatic disease in the liver or lung that may be resectable. Complete resection of oligometastatic foci confined to a single organ can be curative in approximately 25% of these patients. CEA assessment should be done at approximately 6-month intervals. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are recommended annually for up to 5 years postoperatively. PET scanning should not be used for routine surveillance. Colonoscopy is recommended 1 year after resection (or 3 to 6 months after resection if a complete colonoscopy was not done preoperatively) and then in 3 years, followed by every 5 years, unless abnormalities are found.

KEY POINTS

- PET scans should not be used for preoperative staging or postoperative surveillance in colorectal cancer. HVC
- Standard treatment of stages II and III rectal cancer involves chemotherapy, irradiation and surgery, although the optimal sequence is uncertain.
- Patients with rectal cancer who achieve a complete clinical response to chemoradiotherapy may be considered for nonoperative "watch and wait" management.
- Patients with stage II colon cancer that is microsatellite stable or that lacks high-risk features are unlikely to benefit from adjuvant chemotherapy. HVC
- Posttreatment surveillance for patients with colorectal cancer includes periodic history; physical examination; serum carcinoembryonic antigen level testing; and CT of the chest, abdomen, and pelvis, as early detection and resection of isolated metastatic disease can still result in cure.

Metastatic Disease

All metastatic CRCs require molecular analysis for *KRAS*, *NRAS*, and *BRAF* gene mutation status as well as dMMR determination. This step rarely affects the choice of first-line therapy but will define subsequent treatment options. These tests can be done on either the primary tumor or a metastasis; rebiopsy of late-appearing metastases for the purpose of these studies is rarely needed. When sufficient tumor tissue is unavailable, circulating tumor DNA may be assayed in a blood sample (liquid biopsy) for tumor genotyping.

Patients with metastatic disease limited to the liver or lung should be evaluated for surgical resection with curative intent. Unresectable metastatic CRC is treatable but not curable. Although chemotherapy may prolong survival and relieve cancer-related symptoms, patients who have a poor performance status may not benefit or may have unacceptable toxicity.

5-FU is at the center of most treatment regimens, with longer infusions preferable to bolus administration. Leucovorin is often combined with 5-FU. Capecitabine can be an alternative to 5-FU. Other cytotoxic agents used in metastatic CRC include irinotecan and oxaliplatin. The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab is often given concurrently with first-line cytotoxic chemotherapy regimens. This agent potentiates other chemotherapies, resulting in a modestly increased duration of progression-free survival, and in some studies, in increased duration of overall survival. Continuing an anti-VEGF agent with second-line chemotherapy also modestly improves overall survival. Anti-VEGF agents commonly cause hypertension, sometimes requiring therapy. They also impair wound healing and need to be discontinued perioperatively. Very rare but potentially life-threatening adverse effects include arterial thrombotic events such as myocardial infarction, cerebrovascular accidents, and gastrointestinal perforations.

Panitumumab and cetuximab are monoclonal antibodies that bind to and block activation of the epidermal growth factor receptor. They are potentially active only in tumors that harbor nonmutated (wild-type) *KRAS*, *NRAS*, and *BRAF* genes. More recent data suggest that these agents may only have activity in tumors derived from the left side of the large intestine. The major adverse effect of these agents is a painful and socially debilitating acneiform rash. There is a high correlation between rash and antitumor activity, and patients who have only a mild skin rash are unlikely to benefit from these agents. Anti-epidermal growth factor receptor agents should not be used concurrently with anti-VEGF agents, as outcomes are worse. Thus far, immune checkpoint inhibitors have been inactive in metastatic CRC, with the exception of rare metastatic tumors that are dMMR (2% to 4% of all patients with metastases). The programmed death 1 receptor inhibitors pembrolizumab and nivolumab have both shown activity in such patients.

Presently, multigene sequencing beyond *KRAS*, *NRAS*, and *BRAF* offers no clinically useful information and is not warranted outside of a research setting.

KEY POINTS

- 5-fluorouracil (5-FU) is first-line therapy for metastatic colorectal cancer and is often combined with leucovorin; capecitabine is an alternative to 5-FU.
- All metastatic colorectal cancers require molecular analysis for *KRAS*, *NRAS*, and *BRAF* gene mutation status as well as mismatch repair gene deficiency, which will determine treatment after first-line therapy.

Anal Cancer

Anal cancer is a human papillomavirus (HPV)-associated malignancy. Unlike rectal cancer, which is an adenocarcinoma, anal cancer is a squamous cell carcinoma. Anal cancer is often curable with combined irradiation and chemotherapy; surgery is typically not indicated. Mitomycin plus 5-FU or capecitabine is the standard chemotherapy regimen. Although complete regression may be observed as soon as 8 weeks after irradiation, responding tumors may continue to regress for up to 6 months after irradiation. If tumor growth is seen after irradiation, then salvage surgery with a permanent colostomy is indicated. Distant metastases are rare. When they do develop, chemotherapy with a platinum-containing regimen (oxaliplatin, cisplatin, or carboplatin) is often active. Immune checkpoint inhibitors such as nivolumab or pembrolizumab have shown activity in metastatic disease.

Although HPV vaccination would be expected to be as effective at cancer prevention as it is with other HPV-related malignancies, there is no evidence that HPV vaccination plays a role in treatment or posttreatment management of patients with anal cancer. See General Internal Medicine 2 for further discussion of HPV vaccination.

KEY POINT

- Anal cancer, a squamous cell carcinoma linked to human papillomavirus, is often cured by combination irradiation and chemotherapy, sparing the need for surgical resection and colostomy.

Pancreatic Cancer

There are approximately 57,000 patients diagnosed with exocrine pancreatic cancer per year in the United States. Mortality is high, with approximately 46,000 deaths expected annually. Only patients who can undergo a complete resection have a chance of cure. When disease is unresectable because of invasion into critical vascular structures, median survival is approximately 1 year. For those with metastatic disease, median survival is typically less than half that.

Most pancreatic cancers lack a genetic predisposition, although 5% to 10% of patients have either a strong family history of pancreatic cancer, or an identifiable mutation, including *BRCA* gene mutations and dMMR (Lynch syndrome). Genetic counseling and germline testing for *BRCA* and mismatch repair deficiency is now recommended for patients with pancreatic cancer. Chronic pancreatitis, obesity, type 2 diabetes mellitus, high red meat consumption, alcohol abuse, and tobacco use are implicated risk factors.

Painless jaundice, abdominal pain, weight loss, persistent fevers, or protracted nausea and vomiting may be presenting symptoms. Manifestations of hypercoagulability, including Trousseau syndrome (a migratory superficial thrombophlebitis), chronic disseminated intravascular coagulation, deep venous thrombosis, or pulmonary embolism, may be the initial manifestations of underlying pancreatic cancer.

A contrast-enhanced CT of the chest and abdomen (or noncontrast chest CT and abdominal MRI) are appropriate for staging and treatment planning. PET scans do not add value in pancreatic cancer management. Endoscopic ultrasonography may help in staging and is used to more precisely guide diagnostic needle biopsy. Some patients with clinical features that strongly suggest malignancy may not require such preoperative biopsy, as false-negative results would not obviate the need for surgical resection. Magnetic resonance cholangiopancreatography may also be useful in delineating resectability in borderline patients. Conversion therapy—using irradiation or chemotherapy to convert locally unresectable disease to resectable—may be considered in patients in whom a response might create a plane of resection.

Patients without evidence of metastatic disease who appear to have technically resectable disease should undergo resection.

Gemcitabine plus capecitabine or the modified combination regimen of oxaliplatin, irinotecan, 5-FU, and leucovorin are preferred rather than single-agent therapy for patients who have a good performance status and can tolerate aggressive chemotherapy after their surgery. The routine use of postoperative irradiation is not advised.

After pancreatic cancer resection, most patients require pancreatic enzyme replacement therapy, and those with the most extensive pancreatic resection need lifelong insulin therapy.

For metastatic disease, the combination regimen oxaliplatin, irinotecan, 5-FU, and leucovorin or the combination of nab-paclitaxel and gemcitabine have each shown better antitumor activity and modest survival benefits over single-agent gemcitabine, albeit with higher toxicity. In second-line therapy, liposome-encapsulated irinotecan added to 5-FU has shown very modest activity in patients with a good performance status not previously treated with irinotecan.

KEY POINTS

- Patients without metastatic disease who have clinical staging suggesting resectable or borderline resectable pancreatic cancer should undergo resection.
- HVC PET scans do not add value in the staging of pancreatic cancer and are not part of standard management.
- The use of adjuvant chemotherapy with modified oxaliplatin, irinotecan, 5-FU, and leucovorin or gemcitabine plus capecitabine has been shown to increase survival in patients with good postoperative performance status.

Gastroesophageal Cancer

Epidemiology, risk factors, and clinical manifestations of esophageal and gastric cancer are discussed in Gastroenterology and Hepatology.

Upper gastrointestinal tract cancers are a major cause of cancer deaths worldwide, particularly in Asia and Africa. The incidence has been increasing steadily in North America and other Western countries, albeit with changing histology. With the dramatic rise in the incidence of adenocarcinoma of the distal esophagus and proximal stomach, gastroesophageal cancer is now considered a single entity.

Smoking and alcohol use remain the major risk factors for squamous cell carcinoma of the esophagus. Risk factors for the more common adenocarcinoma also include smoking along with gastroesophageal reflux disease (GERD) and obesity. The development of Barrett esophagus as a result of GERD, especially with dysplastic features, is a further risk for developing adenocarcinoma of the esophagus. Surveillance and treatment recommendations are based on grade of Barrett esophagus and the presence of dysplasia. See Gastroenterology and Hepatology for more detailed information on Barrett esophagus and GERD.

Upper endoscopy and biopsy establishes the diagnosis. Endoscopic ultrasonography is routinely used to assess the depth of tumor penetration and presence of involved lymph nodes. In contrast to the evaluation of other gastrointestinal tumors, PET/CT is widely used as part of standard preoperative staging.

Surgery is the primary treatment of locoregional disease, found in approximately one third of patients. Data have shown a survival benefit for preoperative therapy with either neoadjuvant chemotherapy or combined neoadjuvant chemotherapy and radiation therapy. Adjuvant chemotherapy is warranted for patients with cancer who undergo surgery first and whose cancer is more advanced than stage I.

Unfortunately, recurrence rates after surgical resection remain high, even with the use of adjuvant therapy. Treatment of recurrent or metastatic disease is only modestly effective and is not curative.

Approximately 25% of gastroesophageal cancers overexpress the human epidermal growth factor receptor 2 (*HER2*). For patients with metastatic *HER2*-positive gastroesophageal cancer, the addition of the anti-*HER2* monoclonal antibody trastuzumab to chemotherapy provides a modest but statistically significant survival benefit. The anti-VEGF receptor monoclonal antibody ramucirumab has shown modest activity as a non-first-line treatment, either alone or in combination with a taxane. Immune checkpoint inhibitors have shown activity in the non-first-line setting in gastroesophageal tumors with MSI, or, to a lesser degree, in those that are microsatellite stable but express programmed death 1, the target for programmed death 1 inhibitors such as nivolumab or pembrolizumab.

KEY POINTS

- Upper endoscopy and biopsy establishes the diagnosis of gastroesophageal cancer, and endoscopic ultrasonography is routinely used to assess the depth of tumor penetration and presence of involved lymph nodes.
- In contrast to other gastrointestinal tumors, PET/CT is widely used as part of standard preoperative staging of gastroesophageal cancer.
- Upper gastrointestinal tumors should be evaluated for *HER2* overexpression; adding trastuzumab to chemotherapy regimens for patients with *HER2* overexpression and metastatic disease provides a modest survival benefit.

Gastric Lymphoma

The stomach may be the primary site for extranodal lymphoma, a heterogeneous group of B-cell and T-cell neoplasms, generally treated with combination chemotherapy. A specific variant, mucosa-associated lymphoid tissue lymphomas, are indolent tumors; patients often present with localized disease and concomitant *Helicobacter pylori* infection. In that setting, standard treatment to eradicate the *H. pylori* infection results in sustained complete remission in the majority of patients without the need for additional chemotherapy or radiation therapy. Mucosa-associated lymphoid tissue is discussed further in Lymphoid Malignancies.

Neuroendocrine Tumors

Gastrointestinal neuroendocrine tumors (NETs) (formerly called carcinoid tumors) arise from the endocrine cells of the digestive tract. Pancreatic NETs arise from the islets of Langerhans cells and were previously called islet cell tumors. Although histologically similar, gastrointestinal and pancreatic NETs behave differently, with several drugs showing activity against pancreatic NETs but not gastrointestinal NETs. The clinical features of pancreatic NETs are discussed in Gastroenterology & Hepatology.

Most NETs do not produce hormones and are termed "nonfunctional." These tumors are often found incidentally or during the evaluation of metastatic cancer, most commonly to the liver. Up to 25% of NETs may produce hormones that cause symptoms suggesting a diagnosis.

Multiphasic contrast-enhanced CT is used for staging in most patients with NETs except those with low potential to spread. Surgical resection is recommended for localized NETs, and resection may be considered in selected patients with metastatic disease in order to palliate pain or reduce hormone production. Well-differentiated gastrointestinal NETs exhibit indolent growth. Intermediate-grade tumors are generally, but not always, more aggressive, whereas poorly differentiated, high-grade NETs are highly aggressive tumors that are treated with platinum-based cytotoxic regimens used for small cell lung cancer.

Given the indolent nature of metastatic or unresectable NETs, observation and serial examination and imaging, at 3 months initially, then 3 to 6 months subsequently, are appropriate. Asymptomatic patients may do well, with minimal growth and no symptoms for years, even with metastatic disease.

The somatostatin analogues octreotide or lanreotide may be used for hormonal control or to delay tumor progression in patients who have metastatic tumors with somatostatin receptors. Hepatic arterial embolization, radiofrequency ablation, or surgical debulking are sometimes used to decrease hormone production or to relieve symptoms of tumor bulk.

When treatment is needed for either metastatic or unresectable disease, pancreatic NETs can be treated with temozolomide plus capecitabine, or sunitinib (an anti-VEGF tyrosine kinase inhibitor), or everolimus (a mammalian target of rapamycin inhibitor). Everolimus has more modest activity in gastrointestinal NETs, but the other agents used for pancreatic NETs are inactive in gastrointestinal NETs. Peptide-receptor radiotherapy with lutetium 177-labeled somatostatin analogue is a newer approach that is active in well-differentiated NETs and is an appropriate consideration in progressing and/or symptomatic disease.

KEY POINTS

- Although histologically similar, gastrointestinal and pancreatic neuroendocrine tumors (NETs) behave differently, with several drugs showing activity against pancreatic NETs but not gastrointestinal NETs.
- Well-differentiated neuroendocrine tumors are indolent and often initially only require observation and serial imaging. **HVC**

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are sarcomas characterized by an activating mutation in the c-*kit* proto-oncogene, which leads to constitutive activation of the receptor tyrosine kinase. Histologically, GISTs are identified by overexpression of the *KIT* gene, the immunohistochemical marker for KIT protein. Although these tumors may be asymptomatic or incidentally discovered during an endoscopic or imaging procedure, most are associated with nonspecific gastrointestinal symptoms, and some may cause overt bleeding, pain, or signs of obstruction. They are most commonly located in the stomach, which confers a better prognosis, and in the proximal intestine. Other prognostic factors include tumor size and mitotic rate.

For patients undergoing a potentially curative resection of a localized GIST, low-risk tumors do not benefit from further treatment. Higher-risk tumors are treated for 3 years with the adjuvant tyrosine kinase inhibitor imatinib. Imatinib is also used to treat patients who present with unresectable or metastatic disease.

KEY POINT

- High-risk gastrointestinal stromal tumors should be treated with surgery and 3 years of adjuvant imatinib.

Lung Cancer

This section focuses on treatment and follow-up of patients with lung cancer. See Pulmonary and Critical Care Medicine for discussion of epidemiology, screening, clinical manifestations, diagnosis, and staging of patients with lung cancer. Initial biopsy can distinguish tumors as either non–small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC can be divided into pathologic subtypes, including large cell, adenocarcinoma, and squamous cell cancer. These subtypes have characteristic clinical features, and there are some differences in treatment between them, notably for metastatic disease. The staging criteria and treatment of SCLC differ from NSCLC.

Non-Small Cell Lung Cancer

Treatment of NSCLC, similar to that of most other solid malignancies, is based largely on disease stage. For the purposes of this discussion, it is best to divide NSCLC into early-stage, locally advanced, and metastatic categories.

Early-Stage Disease

Early-stage disease refers to lung cancer that is amenable to surgical resection at the time of diagnosis. This typically encompasses stage I and II cancers, although some patients with stage II cancer are not amenable to resection based on location or extent of the primary tumor. Stages I and II are differentiated by hilar nodal metastatic disease and also by the size and invasiveness of the primary tumor into adjacent structures.

Patients deemed potential surgical candidates based on imaging need to have a rigorous functional evaluation to help predict their anticipated pulmonary reserve after surgery. The initial evaluation consists of FEV_1 and DLCO measurement. If both test variables are favorable, then no further evaluation is needed. However, if one or the other variable falls in a range suggesting impaired lung function, then calculation of the predicted postoperative FEV_1 and DLCO should be performed, which is determined by baseline values and assessment of the fractional contribution of the lung to be resected and, in some instances, exercise testing. Based on the results of these assessments, a decision can be made regarding suitability for resection. Patients with pathologic stage I cancer who are undergoing surgical resection have a 60% to 70% survival rate at 5 years, and patients with stage II cancer have approximately a 40% survival rate.

Other options are available for patients who are not surgical candidates, including stereotactic body irradiation that can be used to treat the primary tumor. Such treatments have excellent rates of local control, but they are only suitable for patients with small stage I cancers. For larger tumors, conventional irradiation is used. There are no data supporting the use of chemotherapy combined with irradiation in patients with stage I or II disease. Patients with localized tumors treated with irradiation have a mean survival of greater than 3 years.

Lobectomy is the preferred surgical procedure in early-stage disease. Proximal tumors may be less amenable to lobectomy. In those patients, sleeve resection (resection of the involved lobe and a portion of the main stem bronchus) has fewer postoperative complications and is preferable to pneumonectomy. Sublobar resection can be considered in elderly patients or those with small stage I cancers.

Patients treated surgically for stage I or II disease who have positive margins benefit from postoperative radiation therapy with an improvement in overall survival.

Cisplatin-based adjuvant chemotherapy after resection in patients with resected stage II or III lung cancer results in approximately a 5% decrease in the risk of death at 5 years. Approximately 50% of patients who have surgically resected stage I, II, or IIIA cancer survive 5 years. Chemotherapy consists of cisplatin with a second agent and is typically given for four cycles. The most commonly used chemotherapy partners are vinorelbine, pemetrexed, gemcitabine, and docetaxel.

After treatment is completed, patients with early-stage disease remain at risk for both distant and local recurrence. Many patients with smoking histories are also at risk for developing a second primary lung cancer and cancers of the head, neck, and other sites. Recommendations for surveillance include history, physical examination, and chest CT at least every 6 months for the first 2 years and then annually. Smoking cessation decreases the risk of new primary lung cancers by 20% to 90%; the risk steadily declines beginning 5 years after quitting, but it never quite reaches the incidence found in nonsmokers.

KEY POINTS

- Lobectomy is the preferred surgical procedure in early-stage non–small cell lung cancer.
- Potential surgical candidates with early-stage lung cancer must have FEV_1 and DLCO measurement to predict their anticipated postoperative pulmonary reserve and suitability for resection.
- Patients with early-stage lung cancer who are not surgical candidates can be treated with radiation therapy; stereotactic body irradiation is appropriate for small tumors, but conventional irradiation is used for large tumors.
- Postoperative radiation therapy is used to treat patients with resected localized lung cancer and positive tumor margins; cisplatin-based adjuvant chemotherapy is standard treatment of all resected stage II and III lung cancer.

Locally Advanced Disease

Locally advanced lung cancer is most commonly defined by the presence of clinically detectable lymphadenopathy in the mediastinum or by a primary tumor that invades into local structures, such as the mediastinum, heart, trachea, esophagus, or great vessels.

Improvements in surgical technique and in the accuracy of staging studies have expanded the number of patients eligible for surgical resection, although it is unclear whether this has resulted in improved survival outcomes. For example, some patients with T4 tumors showing invasion into adjacent vital structures, with no evidence of mediastinal node involvement, can have surgical resection and their disease treated as stage III disease. Patients with satellite nodules in the same lobe (T3) or in another ipsilateral lobe (T4) can be resected with curative intent. Even patients with an isolated tumor nodule in the contralateral lung, traditionally considered incurable metastatic disease, can undergo resection to remove all sites of cancer under the assumption that the nodule could represent a second localized primary lung cancer. Finally, patients with limited ipsilateral mediastinal node involvement, a single node station, and non-bulky disease can undergo surgical resection. These patients will all generally receive neoadjuvant or adjuvant chemotherapy or radiation treatment.

Locally advanced lung cancer presenting with bulky or widespread mediastinal or hilar lymph node involvement is generally considered unresectable, so patients are treated with combined platinum-based chemotherapy and irradiation, which has been found to be superior to sequential treatment. Unfortunately, the risk of recurrence, both locoregional and distant, is very high despite chemoradiation treatment (approaching 90%). The use of the anti-programmed death ligand 1 agent durvalumab has been demonstrated to significantly improve overall survival when used after chemotherapy and radiation therapy in patients who have stable disease or objective response after at least two cycles of treatment.

KEY POINT

- Locally advanced lung cancer presenting with bulky or widespread mediastinal or hilar lymph node involvement is generally considered unresectable, so patients are treated with combined platinum-based chemotherapy and irradiation.

Metastatic Disease

Metastatic lung cancer is defined as the spread of disease to distant sites such as the liver, bone, or brain. The presence of one or more tumor nodules in the contralateral lung also qualifies as metastatic disease, but as the prognosis for that pattern of metastatic disease is notably better than that of patients with distant disease, it is classified as M1a, with other distant sites given the designation of M1c. Patients with a solitary site of metastatic disease are classed as M1b. Patients with only a single site of metastatic disease (most frequently in the brain) are potentially curable after resection.

In the past, all patients with metastatic NSCLC were treated with the same chemotherapy regimens. Current treatment options depend on the presence of specific molecular alterations, expression of programmed death ligand 1 (PD-L1) in tumor tissue, and also on histology. The number of available treatments has expanded, and the median survival has improved. Despite these advances, however, metastatic NSCLC remains an incurable disease for most patients. Early palliative care interventions in this patient population will improve quality of life even as they continue to receive aggressive chemotherapy.

Before deciding the optimal treatment for any given patient, it is essential to define histology, assess for molecular alterations, especially for patients with adenocarcinoma, PD-L1 status, and determine performance status. Mutations in the epidermal growth factor receptor gene and for translocations involving *ALK* or *ROS1* should be tested. If an epidermal growth factor receptor mutation is identified, initial treatment with erlotinib or osimertinib is recommended. If an *ALK* or *ROS1* translocation is identified, initial treatment with alectinib is recommended. These agents are small molecule tyrosine kinase inhibitors that are specific for those genetic alterations. There are data and approved agents for the treatment of other molecular abnormalities in lung cancer, for example, BRAF V600E mutations, TRK, and c-Met. The list of targetable mutations and translocations is expanding rapidly, and there is an emerging consensus that all patients with advanced NSCLC should have their tumors tested by next-generation sequencing. Next-generation sequencing uses parallel sequencing of multiple small fragments of DNA to determine genome sequence and can be performed on blood leukocytes or a variety of other sources.

Immunotherapy targeting programmed death 1 or PD-L1 has transformed treatment of metastatic NSCLC. It can be combined with platinum-based combination chemotherapy in the front-line treatment setting for both adenocarcinoma and squamous cell carcinoma. It can also be used as a single agent in the front-line setting or after prior treatment with chemotherapy. Combining chemotherapy and immunotherapy has been shown to improve survival regardless of PD-L1 status, although it also increases risk of adverse effects. Single-agent immunotherapy, however, is only appropriate for patients with adequate PD-L1 tumor expression. In the front-line setting, pembrolizumab improves response rate, progression-free survival, and overall survival if PD-L1 expression is 50% or higher. Other reports have found 5-year survival rates of 25% to 30% in patients treated with pembrolizumab in the front-line setting when PD-L1 expression is at least 50%. It is also FDA approved for use in patients with PD-L1 expression from 1% to 49%, although it is less active as a single agent for such patients.

Patients without a relevant molecular alteration and who are not candidates for immunotherapy are treated with platinum-based chemotherapy. Cisplatin is slightly more active, but carboplatin is commonly used because of its more favorable adverse effect profile. Histologic assessment can help guide choice of the second agent, as patients with adenocarcinoma have been shown to respond well to pemetrexed, whereas those with squamous cell carcinoma respond better to gemcitabine. Chemotherapy is administered for four to six cycles. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, can be added to platinum-based chemotherapy in patients not treated with immunotherapy. It provides only modest improvement in progression-free survival and overall survival. It carries the risk of thrombosis, stroke, myocardial infarction, and hemoptysis in some patients. It is not indicated in patients with squamous cell carcinoma due to risk of hemoptysis. For patients who respond to front-line chemotherapy, maintenance treatment with docetaxel, pemetrexed, or gemcitabine has been shown to improve progression-free survival, and pemetrexed has also been shown to improve overall survival.

Stereotactic body irradiation can be used to treat residual metastatic sites after response to systemic therapy. Progression-free survival is improved compared with maintenance chemotherapy alone. It can also be used to treat isolated or limited areas of disease progression in patients receiving otherwise active systemic therapy.

Patients with poor performance status do not benefit from chemotherapy or immunotherapy and should be considered for hospice care.

KEY POINTS

- HVC Patients with poor performance status do not benefit from chemotherapy or immunotherapy and should be considered for hospice care.
- Metastatic non–small cell lung cancer that demonstrates an epidermal growth factor receptor gene mutation should be treated initially with erlotinib or osimertinib; if an *ALK* or *ROS1* translocation is identified, initial treatment should be with alectinib.
- If metastatic non–small cell lung cancer is negative for a driver mutation, treatment options include immunotherapy, platinum-based chemotherapy, or a combination of both.

Small Cell Lung Cancer

SCLC, a neuroendocrine neoplasm, currently accounts for approximately 10% of lung cancer cases. SCLC is almost exclusively caused by smoking. Most patients initially present with distant metastatic disease. SCLC can be associated with paraneoplastic syndromes, most prominently the syndromes of inappropriate antidiuretic hormone secretion and Lambert-Eaton myasthenia. Although the staging system used for SCLC is the same as that for NSCLC, most therapeutic decisions are made based on whether patients have “limited disease,” usually defined as disease limited to the hemithorax and regional lymph nodes and can be safely encompassed in a radiotherapy field (stage I–IIIb). All others, including those with distant metastases, have “extensive disease” (stage IV). Patients should undergo a routine CT of the thorax, abdomen, and pelvis, but even those who have no bone or central nervous system symptoms should undergo a PET or whole-body bone scintigraphy and an MRI of the brain, as asymptomatic metastases are not uncommon.

Typically, patients with primary SCLC present with proximal and often large tumors, but occasionally exhibit a solitary pulmonary nodule (see Pulmonary and Critical Care Medicine). They are often not diagnosed until after surgical resection. After resection, these rare patients should be treated with adjuvant chemotherapy, but radiation therapy can be avoided if surgical margins are negative. Surgery can also be performed for small primary tumors without lymph node spread, although preoperative evaluation in those patients should include endobronchial ultrasonography or mediastinoscopy to rule out occult nodal involvement. Those patients should also receive adjuvant chemotherapy.

Most patients with SCLC will not meet the criteria for primary surgery. Treatment of limited disease consists of combined cisplatin-based chemotherapy, typically cisplatin plus etoposide, and irradiation. Chemotherapy is continued after irradiation for up to six cycles; prophylactic cranial irradiation can be used in patients with responsive disease to decrease the rate of subsequent brain metastases and improve overall survival. This treatment increases risk of cognitive impairment in patients 60 years and older, however, and is not indicated in patients with poor performance or those with pre-existing neurocognitive impairment.

For patients with extensive disease, treatment consists of combination platinum-etoposide and immunotherapy without irradiation for up to six cycles with continuation of immunotherapy until progression. Patients with lower-volume disease that is responsive to treatment and without brain metastases can be considered for prophylactic cranial irradiation. Patients with extensive disease who have a favorable response to chemotherapy but persistent involvement in the lung can be treated with additional radiation therapy.

Despite treatment response, recurrences are very common, even in patients with limited disease at the time of diagnosis. For patients with recurrent disease who had a disease-free interval of more than 3 months, treatment with the initial platinum-based doublet regimen can be used because the likelihood of response is favorable. However, for patients who relapse earlier, treatment with different agents is indicated. Although immunotherapy has been shown to be beneficial in this setting, the results are not as remarkable as in patients with NSCLC. As in NSCLC, addressing goals of care and aggressive symptom management are of significant importance in this setting.

KEY POINTS

- Routine staging of patients with small cell lung cancer includes CT scan of the thorax, abdomen, and pelvis as well as PET or whole-body bone scintigraphy and MRI of the brain.
- Patients with early-stage disease (stage I) small cell lung cancer can be considered for resection and adjuvant chemotherapy without irradiation if surgical margins are negative.
- Patients with both limited- and extensive-stage small cell lung cancer who respond to chemotherapy should consider prophylactic irradiation to the central nervous system.

Head and Neck Cancer

Squamous cell carcinoma is the most common form of head and neck cancer, including primary tumors of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinuses, thyroid, and salivary glands. Thyroid cancer is discussed in Endocrinology and Metabolism.

Risk Factors

The most important risk factor for head and neck cancer is smoked and smokeless tobacco use. Alcohol use is also a known risk factor, and the combination of alcohol and tobacco synergistically increases the risk.

Human papillomavirus (HPV) is an increasingly important cause of head and neck cancer, with most HPV-associated cancers arising in the tonsils or base of the tongue. Although treatment is not altered, the prognosis of HPV-associated oropharynx cancer in nonsmokers is significantly better than that for non–HPV-related cancer.

KEY POINTS

- Tobacco and alcohol use are important risk factors for head and neck cancer, and their combined use synergistically increases risk.
- Human papillomavirus (HPV) infection is an important cause of oropharyngeal cancer; in nonsmokers, the prognosis is better than that for non–HPV-related cancer.

Clinical Manifestations

Presenting symptoms vary with the cancer's location, but concerning signs and symptoms include persistent or progressive lymph node enlargement or other neck mass, unilateral hearing loss or ear pain, nasal obstruction, oral pain, nonhealing oral ulcers, dysphagia, odynophagia, and hoarseness. HPV-related oropharynx cancers commonly present with a painless neck mass, sometimes arising rapidly, and are often cystic on ultrasonography.

Evaluation and Staging

Initial evaluation of patients suspected of having head and neck cancer includes history and physical examination. Infection should be suspected in patients with a rapidly developing neck mass, particularly in the setting of upper respiratory symptoms or with typical physical findings of infection, such as warmth, tenderness, and erythema. In contrast, malignant neck masses are commonly painless, firm, and/or fixed on examination and not associated with antecedent infection. If malignancy is a potential concern, prompt referral to an otolaryngologist for assessment and direct laryngoscopy is essential. Fine-needle aspiration of suspicious neck masses is accurate for diagnosis of squamous cell carcinoma. Tumor staining for p16, which is overexpressed in HPV-positive cancers, is standard for oropharynx cancers.

When a diagnosis of malignancy has been established, imaging studies are indicated for accurate assessment of the extent of local disease and evaluation of nodal and distant metastatic disease. MRI is preferred for assessment of the primary tumor. PET/CT is useful to evaluate regional nodes and rule out distant metastatic disease, although it is not accurate in nodes 5 mm or smaller.

The staging of head and neck cancers is complex, as each subsite uses a different staging system. Stage is the most important determinant of prognosis. Staging of primary tumors is based on both size and extent of invasion into adjacent structures. Nodal staging is predicated on the number of nodes involved, size, and presence or absence of bilateral lymphadenopathy. HPV-related cancer of the oropharynx has a different staging system than non–HPV-related cancer based on significant differences in prognosis. Patients with early-stage head and neck cancers have 70% to 90% long-term survival. Multimodality tumor board discussion is valuable for determining the proper course of treatment.

KEY POINT

- Malignant neck masses are commonly painless, firm and/or fixed on examination, and not associated with antecedent infection.

Treatment

Approximately one third of patients who present with small tumors without lymph node metastases are effectively treated with either surgery or radiation therapy. Treatment decisions weigh tumor location and postoperative complications, including appearance and preservation of speech, with the expected morbidity of radiation therapy, including acute mucositis and fatigue, along with more long-lasting alterations in taste, xerostomia, dental disease, and an increased risk of second malignancies. Additional dissection of lymph nodes in the neck is determined by the site and stage of the primary tumor, presence of enlarged nodes, and the results of diagnostic imaging.

Adjuvant irradiation for patients with primary surgical resection is recommended for those with one or more high-risk pathology features (**Table 10**). Combined chemotherapy, typically single-agent cisplatin, and irradiation can be used for patients felt to be at very high risk for recurrence, especially with extracapsular extension or positive or close margins.

TABLE 10. High-Risk Pathologic Features in Head and Neck Cancer

T3 or T4 tumor
Positive resection margins
Lymph node extracapsular extension
≥2 positive lymph nodes (N2 or N3)
Perineural invasion
Lymphovascular invasion

Data from Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. J Natl Compr Canc Netw. 2018;16(5):479-90. [PMID:29752322]

Radiation therapy and larynx-sparing surgery, consisting of either transoral laser surgery or open partial laryngectomy, offer equivalent survival benefit in patients with early-stage laryngeal cancer. These treatments focus on attaining optimal survival and function of voice, swallowing, and airway mechanics. For patients with an unresectable primary tumor or extensive nodal disease, initial treatment with combined chemotherapy, either cisplatin or cetuximab, a monoclonal epidermal growth factor receptor antibody, and irradiation is recommended. Surgery is reserved for treatment of persistent disease or in the setting of inadequate response to treatment.

Treatment of nasopharyngeal carcinoma with irradiation alone can be used with excellent outcomes in patients with very early-stage disease. For all other patients, however, treatment consists of combined chemotherapy and irradiation.

KEY POINT

- Patients with small head and neck tumors without lymph node metastases are effectively treated with either surgery or radiation therapy.

Posttreatment Surveillance

After treatment of localized disease, a history and physical examination, including laryngopharyngoscopy, should be conducted every 1 to 3 months for the first year after primary treatment, decreasing in frequency thereafter, with annual evaluation 5 years and beyond. Patients treated with radiotherapy that includes the thyroid bed are at risk for hypothyroidism and thyroid carcinoma. Periodic assessment of thyroid function and a physical examination of the thyroid are indicated, although thyroid ultrasonography should not be performed. Similarly, repeated PET/CT or other imaging surveillance following a negative posttreatment scan is not indicated in the absence of worrisome signs or symptoms.

Up to 20% of head and neck cancer survivors develop a second primary cancer related to smoking and alcohol exposure. In addition to lifestyle modification, screening for lung cancer should be implemented in persons at increased risk.

KEY POINTS

HVC
- Routine imaging for head and neck cancer after a negative posttreatment scan is not indicated unless signs and symptoms suggest recurrent disease.

HVC
- Although patients who receive radiation therapy that includes the thyroid bed are at increased risk of thyroid cancer, screening thyroid ultrasonography is not indicated.

Management of Recurrent Head and Neck Cancer

Recurrent head and neck cancer is curable in selected patients, such as those with small localized lesions and a long disease-free interval. Patients with limited recurrence are treated with surgery and adjuvant therapy as needed. For patients with unresectable local recurrence, treatment with irradiation or chemoradiation is appropriate in some cases. Reirradiation can be associated with long-term survival but also with a potentially significant risk of toxicity including pain, tissue necrosis, infection, and fatal bleeding.

For patients with distant metastatic disease or unresectable persistent local disease not amenable to surgery or irradiation, systemic therapy is the mainstay of treatment. The current standard front-line treatment is either a combination of platinum-based chemotherapy and pembrolizumab, or in patients with programmed death ligand 1–positive cancer, use of pembrolizumab alone. Patients with distant metastases and unresectable local disease have a poor prognosis, especially if their performance status is declining; treatment decisions should include options for palliative and hospice care.

KEY POINTS

- Patients with small, localized recurrent head and neck cancer following a long disease-free interval may be cured with additional surgery and adjuvant therapy.
- Patients with advanced head and neck cancer not amenable to surgery or irradiation should first receive a combination of platinum-based chemotherapy and pembrolizumab, or pembrolizumab alone in patients with programmed death ligand 1–positive cancer.

Genitourinary Cancer

Prostate Cancer

Epidemiology and Risk Factors

Adenocarcinoma of the prostate remains one of the most commonly diagnosed types of cancer among men in the United States. Age is a very important risk factor; prostate cancer is rarely diagnosed before age 40 years, but after that point, the incidence increases significantly. Ethnicity is also an important risk factor, with the incidence greater for Black men than for White or Hispanic men. Further, Black men are more likely to be diagnosed at a younger age with higher-risk disease. Genetics and family history also play an important role in risk. Men with a first-degree relative diagnosed with prostate cancer are twice as likely to be diagnosed. Prostate cancer is also linked with germline mutations in different genes, such as *BRCA1* and *2*, *ATM*, *CHEK2*, *HOXB13*, and the Lynch syndrome genes, among others.

Diagnosis and Staging

Prostate cancer is most commonly diagnosed after identification of an elevated serum prostate-specific antigen (PSA) level during screening and in the absence of symptoms. See General Internal Medicine 2 for a discussion of current issues relating to prostate cancer screening.

Although urinary symptoms might be present in patients with prostate cancer, they are usually related to benign prostatic hyperplasia. In some men with metastatic disease at the time of initial presentation, bone pain or back pain can be the presenting symptom. If the diagnosis is suspected on the basis of an elevated serum PSA level, the elevation should first be confirmed by a second measurement at least 1 month later. Persistent serum PSA elevation should prompt urology referral, as should an abnormal finding in the prostate on digital rectal examination (DRE).

Prostate biopsy is performed using transrectal ultrasonography for guidance, and several cores should be taken from different regions of the gland. Most commonly, at least five to seven cores are taken per side to provide a sufficient diagnostic yield. Atypical small acinar proliferation and multifocal high-grade prostatic intraepithelial neoplasia are both associated with a high risk of underlying cancer and should prompt rebiopsy.

Risk stratification using serum PSA, Grade Group (based on Gleason score), and TNM cancer staging based on biopsy results and DRE determines prognosis and treatment options (**Table 11**). Imaging studies need not be done in patients whose risk is very low or low but should be obtained in others to evaluate regional lymph node involvement and metastatic disease. Genetic testing for *BRCA* gene mutation should be done in all men with high-risk disease, including patients with positive lymph nodes or metastatic disease. The risk of an underlying mutation in patients with metastatic disease is 11.8%.

KEY POINT

- Genetic testing for *BRCA* gene mutation is recommended for all men with high-risk prostate cancer, including patients with positive lymph nodes or metastatic disease.

TABLE 11. Prostate Cancer Risk Stratification

Risk Category	Definition[a]
Very low/low	Stage T1-T2a, serum PSA <10 ng/mL (10 µg/L), Grade Group 1 (Gleason 3+3)
Intermediate	T2b-T2c OR Grade Group 2-3 (Gleason score 7) OR PSA 10-20 ng/mL (10-20 µg/L)
High	T3a OR Grade Group 4-5 (Gleason score 8-10) OR PSA >20 ng/mL (20 µg/L)
Very high	T3b-T4, primary Gleason pattern 5, >4 cores with Grade Group 4-5

PSA = prostate-specific antigen.

[a] T1 tumors are not palpable or seen on imaging; T1a (<5% of specimen) and T1b (>5% of specimen) are discovered incidentally in a pathologic specimen resected for benign disease; T1c is discovered in prostate biopsy for elevated serum PSA.

T2 tumors are palpable; T2a involves <50% of one lobe; T2b involves >50% of one lobe; T2c are in both lobes of the prostate.

T3a tumors extend through the prostate capsule; T3b involves the seminal vesicles.

T4 tumors are fixed to adjacent structures.

Data from NCCN Clinical Guidelines in Oncology. Prostate Cancer. Version 2.2019. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 14, 2019.

Treatment

Treatment options for men with newly diagnosed localized prostate cancer include active surveillance, irradiation, and radical prostatectomy. For men with limited life expectancy or significant medical comorbidities, observation is most appropriate.

Active surveillance is deferral of curative-intent therapy in lieu of regular monitoring for evidence of disease progression. It is an option for men with very-low-risk or low-risk prostate cancer who have a life expectancy of at least 10 years. Active surveillance should consist of DRE (not more than every 12 months), serial measurement of serum PSA (assessing level changes and calculating PSA doubling time), and repeat biopsy. Repeat biopsy is typically done at 1 year, and if no high-grade disease is identified, it can be done less often after that. A PSA doubling time of less than 3 years warrants an additional prostate biopsy. Fifteen-year metastasis-free survival is as high as 97% in appropriately selected patients.

Active treatment of low-risk localized prostate cancer is typically a choice between external beam irradiation and radical prostatectomy. Brachytherapy, in which radioactive implants are inserted into the prostate, is also an option for men with low-risk cancer or selected men with low-volume intermediate-risk cancer.

Irradiation is associated with short-term risks of enteritis (approximately 20% of men) and cystitis (approximately 50% of men). These conditions become long-term complications in a very small percentage of patients. Erectile dysfunction typically increases over time after irradiation, such that by 2 years, approximately 60% to 70% of men have at least moderate erectile dysfunction. However, a recent series found similar rates of decline in men treated with active surveillance.

With radical prostatectomy, the main risks are urinary incontinence and erectile dysfunction. Urinary incontinence is relatively common immediately after surgery. The rate of chronic moderate to severe incontinence is approximately 5% to 10%. Erectile dysfunction is relatively common after surgery and can persist for several years. Approximately 40% of men reported erectile dysfunction 2 years after surgery.

A large study showed no difference in survival after 10 years for patients with localized prostate cancer detected through serum PSA screening who were randomized to receive active surveillance, surgery, or radiation therapy. There was a trend toward improved survival for patients older than 65 years who received either of the active interventions. Patients receiving surgery or irradiation had decreased disease progression and decreased metastatic disease.

For men with intermediate-risk or higher-risk localized disease who are treated with radiation therapy, the addition of a gonadotropin-releasing hormone (GnRH) agonist will delay disease progression. It has also been shown to improve overall survival in men with high-risk and very-high-risk prostate cancer.

After definitive local treatment, men are monitored for evidence of recurrence with serial serum PSA measurements every 3 to 4 months and DRE yearly, although DRE can be omitted if PSA is undetectable. After radical prostatectomy, the PSA should rapidly become undetectable, but after radiation treatment, the PSA will fall gradually and reach a nadir but will not necessarily become undetectable. PSA recurrence after surgery is defined as a detectable PSA level that increases on at least two measurements; after irradiation, PSA recurrence is defined as an increase in the PSA level by at least 2 ng/mL (2 µg/L) above the nadir PSA.

For men with PSA-only recurrence, an evaluation to look for evidence of clinical local or metastatic disease with imaging studies is indicated. If men were treated with initial surgery, and metastatic disease has not been identified, salvage irradiation with or without androgen deprivation therapy (ADT) can be offered. Likewise, if men were treated initially with irradiation, local therapy (such as surgery or cryotherapy) can be offered, provided a transrectal ultrasound-guided biopsy specimen is positive and no metastatic disease is identified. If the result of the specimen is negative, then ADT can be considered. Men with metastatic disease can also be treated with ADT, although the benefit in that setting is uncertain.

ADT results in many short-term and long-term adverse effects. Short-term effects include loss of lean body mass, fatigue, gynecomastia, hair loss, decreased libido, erectile dysfunction, and vasomotor symptoms. Long-term risks include a possible increase in cardiovascular disease, increased risk of venous thromboembolism, and reduction in bone density. All men being treated with ADT should take supplemental calcium and vitamin D, and baseline fracture risk assessment is recommended using a dual-energy x-ray absorptiometry scan, although the impact on outcomes is uncertain.

For men with PSA recurrence, with or without clinical metastatic disease, observation is a reasonable consideration depending on patient and disease-specific factors, such as symptoms and PSA doubling time. This is especially true for men with PSA-only recurrence. For such men with a rapid doubling time (<10 months), treatment is generally recommended; however, men with a slow PSA doubling time (>10 months) do not require immediate treatment because it can take several years for clinical metastatic disease to develop in that setting.

KEY POINTS

- Treatment options for men with newly diagnosed localized prostate cancer include active surveillance, irradiation, and radical prostatectomy.
- Gonadotropin-releasing hormone agonist therapy is typically administered with radiation therapy for localized intermediate- or high-risk prostate cancer.
- HVC Patients with PSA-only recurrence of prostate cancer may be treated with androgen deprivation therapy, although observation is also a reasonable choice.

Metastatic Prostate Cancer

Once distant metastatic disease is diagnosed, the mainstay of therapy is ADT. Options for providing ADT include orchiectomy, GnRH-agonist therapy (with or without antiandrogen), and GnRH-antagonist therapy (**Table 12**). Psychological aversion to orchiectomy has limited its use in the United States, although it is a rapidly acting and cost-effective way to achieve androgen depletion.

In patients who have clinical metastatic disease, short-term antiandrogen therapy should precede or be started at the same time as a GnRH agonist, and the combination should be continued for at least 7 days because of the risk of a transient worsening of disease-related symptoms, termed a flare reaction. Initial anti-androgen therapy is not necessary if a GnRH antagonist is used. Intermittent ADT is not typically recommended in men with clinical metastatic disease, although it can be offered to mitigate adverse effects. Response can be assessed most easily by serial serum PSA measurement, but imaging also plays a role. The serum testosterone level should be less than 50 ng/dL (1.7 nmol/L) in men treated with ADT.

Men with clinical metastatic disease who respond to ADT are considered to have castrate-sensitive prostate cancer. In this population, ADT can be combined with docetaxel, abiraterone/prednisone, enzalutamide, or apalutamide to improve survival. Irradiation to the primary tumor can also be considered for men with low-volume metastatic M1 disease.

After identifying progressive disease in men being treated with ADT (castrate-resistant prostate cancer), many treatment options exist (see Table 12). Osteoclast inhibitors (bisphosphonates or denosumab) will reduce bone pain and lower fracture risk in men with castrate-resistant, metastatic prostate cancer and should be routinely prescribed. Initial treatment options for castrate-resistant prostate cancer include docetaxel with prednisone, abiraterone with prednisone, enzalutamide and, for symptomatic bone metastases, radium-223. Patients with M0 (without evidence of distant metastasis) castrate-resistant disease do not clearly require treatment. The decision to treat is based on PSA doubling time among other factors. For men with a rapid doubling time, both enzalutamide and apalutamide are effective. For patients who develop progressive disease, a different agent can be used. Cabazitaxel, a chemotherapy agent, can be combined with prednisone for patients who have cancer progression after treatment with docetaxel. Pembrolizumab can be used for select patients characterized by high levels of microsatellite instability or deficient mismatch repair after progression on front-line therapy and absence of an alternative treatment.

KEY POINTS

- Continuous androgen deprivation therapy (ADT), including orchiectomy, gonadotropin-releasing hormone–agonist therapy, and gonadotropin-releasing hormone–antagonist therapy, is most appropriate for metastatic prostate cancer.

(Continued)

TABLE 12. Treatments for Metastatic Prostate Cancer

Class	Agents	Mechanism of Action	Indications
GnRH agonist	Leuprolide, goserelin, triptorelin, buserelin, histrelin	Binds to GnRH receptor, causes initial release of FSH/LH (and also testosterone) followed by suppression	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
GnRH antagonist	Degarelix	Binds to GnRH receptor and suppresses activity without initial increase in activity seen with GnRH agonists	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
Antiandrogen	Bicalutamide, flutamide	Binds to androgen receptor with competitive inhibition of testosterone binding	Metastatic castrate-sensitive prostate cancer (not indicated as monotherapy, only in combination with GnRH agonist or antagonist)
CYP17 inhibitor	Abiraterone plus prednisone	Blocks androgen synthesis in tumor tissue, testes, and adrenal glands	Metastatic castrate-resistant prostate cancer; used in combination with prednisone as it can cause adrenal insufficiency
Androgen receptor blockade	Enzalutamide	Binds to the androgen binding site of the androgen receptor in a noncompetitive fashion	Metastatic castrate-resistant prostate cancer and M0 castrate-resistant prostate cancer
Androgen receptor blockade	Apalutamide	Same as enzalutamide	M0 castrate-resistant prostate cancer
Tumor vaccine	Sipuleucel-T	Autologous dendritic cell therapeutic vaccine Aims to increase T-cell response to prostatic acid phosphatase	Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer with no visceral metastatic disease Not indicated for PSA-only relapse; does not result in PSA response
Bone-seeking isotope	Radium-223	Alpha particle–emitting isotope that concentrates in bone	Metastatic castrate-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease
Chemotherapeutic	Docetaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer with clinical metastatic disease Metastatic castrate-sensitive prostate cancer in combination with ADT in men with clinical metastatic disease Adjuvant therapy after radiation in men with high-risk or very-high-risk prostate cancer, in combination with ADT
Chemotherapeutic	Cabazitaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer following disease progression after docetaxel treatment

ADT = androgen-deprivation therapy; CYP17 = 17α-hydroxy/17,20-lyase; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; M0 = without evidence of distant metastasis; PSA = prostate-specific antigen.

KEY POINTS ***(continued)***

- Men with metastatic prostate cancer who respond to ADT and then receive docetaxel abiraterone/prednisone, enzalutamide, or apalutamide will have improved survival.
- All men who are treated with ADT should take supplemental calcium and vitamin D.
- Osteoclast inhibitors will reduce bone pain and lower fracture risk in men with castrate-resistant, metastatic prostate cancer.

Testicular Cancer

Testicular cancer is the most common solid tumor diagnosed in men aged 15 to 35 years, although it accounts for only about 1% of all cancers diagnosed in the United States. It is also one of the most curable forms of cancer, due in large part to its sensitivity to chemotherapy. Patients most commonly present with a unilateral testicular swelling or mass.

Patients with localized symptoms should have a scrotal ultrasound and baseline tumor markers, including α-fetoprotein and β-human chorionic gonadotropin. Diagnosis is made most commonly through radical inguinal orchiectomy. Needle biopsy of a testicular mass is contraindicated because of concern regarding tumor seeding to the scrotum and inguinal nodes. When the diagnosis is confirmed, evaluation with chest radiography, CT of the abdomen and pelvis, and tumor marker levels after orchiectomy are used for staging. Marker levels fall at predictable rates after surgery, and sufficient time is needed before concluding that markers remain elevated after orchiectomy.

Histologically, testicular cancers are either pure seminomas or nonseminomatous germ cell tumors. Tumors with seminoma pathology but elevated α-fetoprotein levels are termed mixed germ cell tumors and are managed as a nonseminomatous germ cell tumor. Management depends on histology, the results of staging studies, and the presence or absence of serum tumor marker elevation after orchiectomy. It is essential to discuss and offer sperm cryopreservation before initiating additional treatment.

For pure seminoma, active surveillance can be offered after surgery for early-stage disease; adjuvant irradiation or chemotherapy with one to two cycles of carboplatin are also appropriate options. Stage II seminoma is defined by retroperitoneal lymph node metastases. These patients can be treated with either irradiation to the paraaortic lymph nodes and superior ipsilateral pelvis or chemotherapy, depending on the extent of lymph node involvement. Patients with more extensive lymph node involvement should receive chemotherapy. For higher-stage disease, cisplatin-based chemotherapy is used. PET/CT can be used to determine whether residual masses after chemotherapy require resection. Residual masses that show negative results on PET scan may be benign and can be followed, with resection based on any further increase in size. Residual masses that show positive results on PET scan should be promptly resected, as cure remains possible.

After resection, patients with early-stage nonseminomatous germ cell tumors can be managed with active surveillance (in selected patients), retroperitoneal lymph node dissection (RPLND), or limited chemotherapy. Adjuvant chemotherapy is recommended in patients with nodal involvement on RPLND. Persistence of tumor marker elevation after orchiectomy without abnormal imaging findings is also an indication for chemotherapy. Some patients with clinically metastatic retroperitoneal nodes can be managed with RPLND or primary chemotherapy if markers are negative and nodal metastases are limited and small. For patients with several positive nodes, large nodes (>5 cm), or elevated markers, chemotherapy is recommended. Any residual masses after chemotherapy should be resected.

For the first year after treatment, patients should be clinically evaluated every 2 to 3 months and should have tumor marker measurement and imaging studies periodically, with specific intervals determined by histology, stage, and previous treatment. After the first year, evaluations can be performed less often.

Patients with recurrent disease are treated and may well be cured with combination chemotherapy or high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

Men treated with chemotherapy for testicular cancer are at risk for many different long-term complications, including cardiovascular disease, metabolic syndrome, pulmonary toxicity, hypogonadism, infertility, chronic kidney disease, and neurotoxicity. The risk of a second solid tumor is approximately twofold higher than in men without a history of testicular cancer.

KEY POINTS

- Measurement of α-fetoprotein and β-human chorionic gonadotropin is important before and after inguinal orchiectomy for staging and prognosis of testicular cancer.
- Patients with stage II seminoma can be treated with adjuvant irradiation or cisplatin-based chemotherapy, although chemotherapy is preferred with more extensive lymph node involvement.
- Patients with seminoma and residual masses that show negative results on PET scan can be followed, with resection based on any further increase in size; masses that show positive results on PET scan should be resected.
- Patients with nonseminoma and clinically metastatic nodes can be treated with retroperitoneal lymph node dissection or chemotherapy; chemotherapy is preferred if there are several positive nodes, large nodes (>5 cm), or elevated serum tumor markers.

Renal Cell Carcinoma

Renal cancers typically arise in the cortex of the kidney. The most common histology is clear cell carcinoma, which is also the most responsive to medical treatment. In the past, the most common presenting symptoms of renal cell carcinoma were hematuria, abdominal mass, and weight loss, but most patients are currently diagnosed incidentally based on imaging studies done for other reasons. Ultrasonography can be used to differentiate benign cysts from complex cysts or solid masses. If a lesion is not clearly a benign cyst, CT is indicated for further evaluation. Patients with CT findings pathognomonic for renal cell cancer do not need a confirmatory renal biopsy to establish the diagnosis.

Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases (known as Stauffer syndrome), fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica. Many of these conditions can improve with resection of the primary tumor, metastatic sites, or both.

A suspicious solitary renal mass less than 4 cm does not necessarily require treatment. Active surveillance is an option for such lesions. Treatment can be either with surgery or ablation, most commonly cryoablation. Larger lesions require surgical treatment. This consists of either radical nephrectomy or partial nephrectomy, depending on the size and location of the primary tumor. At the present time, adjuvant therapy is not recommended. Although sunitinib has been approved by the FDA as an adjuvant therapy following surgery, its effect on survival has not been consistently proven and it is associated with significant toxicity. Postoperative surveillance to identify recurrent disease is indicated, with the frequency of interventions depending on the extent of local disease. This typically consists of a history and physical examination, basic laboratory studies, and imaging of the chest and abdomen.

Resection or debulking of the primary renal cell cancer improves survival for select patients with metastatic disease. Surgery or other local therapies (such as stereotactic radiation therapy) also have a role in the treatment of isolated or several easily resected areas of metastatic disease.

No specific front-line therapy has been shown superior for patients who present with metastatic clear cell or non-clear cell histology. Various agents, including immune checkpoint inhibitors and tyrosine kinase inhibitors, have been shown to be effective. Combination therapy with axitinib, a vascular endothelial growth factor inhibitor, and the immune checkpoint inhibitor pembrolizumab has been shown as effective in the front-line setting.

KEY POINTS

HVC
- Patients with CT findings pathognomonic for renal cell carcinoma do not need a biopsy to confirm the diagnosis.
- Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases, fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica.
- Resecting or debulking a primary renal cell cancer may improve survival in select patients with metastatic disease.

Bladder Cancer

Bladder cancer is the most common cancer of the genitourinary tract. Most patients have transitional cell carcinoma, which is the focus of this section. Common presenting symptoms include hematuria and irritative urinary symptoms.

It is important to assess for gross hematuria in review of systems questioning for all patients and confirm with a urinalysis if a patient does note hematuria. Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have persistent microscopic hematuria after evaluating benign causes, such as urinary tract infection, nephrolithiasis, or underlying kidney disease with a glomerular source of erythrocytes. Notably, use of anticoagulants does not alter these recommendations.

The primary modality of initial evaluation is cystoscopy, with biopsy of any visible tumor or mucosal abnormality. Random biopsy is performed if no abnormality is seen. If cancer is confirmed, then transurethral resection of the bladder tumor (TURBT) and examination under anesthesia is performed to determine histology and depth of invasion.

Most patients are found to have non–muscle invasive disease. This can include exophytic lesions (Ta, which can be low grade or high grade), carcinoma in situ (Tis, always high grade), or early-stage invasive cancer (T1). Small low-grade Ta tumors are treated with TURBT followed by observation or intravesical chemotherapy. All other noninvasive disease is treated with TURBT followed by either intravesical bacillus Calmette-Guérin or intravesical chemotherapy. After primary treatment, cystoscopic surveillance is indicated because of the risk for recurrent disease. There is a higher risk for muscle invasive recurrence for patients with larger tumors, less differentiated tumors, tumors that invade into the lamina propria, and tumors with multifocal or noninvasive recurrence. Most patients require cystoscopy 3 months after initial therapy, with subsequent cystoscopy at periodic intervals based on risk of recurrence. Cystectomy can be considered for patients at high risk for developing muscle-invasive disease.

If muscle-invasive disease is diagnosed, imaging studies are indicated for staging. Cystectomy is indicated, with or without neoadjuvant cisplatin-based chemotherapy. Partial cystectomy can be considered in very carefully selected patients. For patients unable or unwilling to undergo cystectomy, maximal TURBT can be combined with concurrent chemoradiotherapy for those with limited disease. Adjuvant chemotherapy after surgical resection is appropriate to consider in patients with high-risk features, such as positive nodes and extension beyond the bladder.

Treatment of metastatic disease requires systemic therapy, and treatment outcomes remain poor. Cisplatin-based combination chemotherapy remains the evidence-based choice, although immune checkpoint treatment can be given to patients with programmed death ligand 1–positive cancers. After further progression, single-agent therapy with either chemotherapy or an immune checkpoint inhibitor is recommended.

KEY POINTS

- Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have microscopic hematuria in the absence of an apparent benign cause; use of anticoagulants does not alter these recommendations.
- Superficial bladder cancer does not invade the muscle, and treatment includes transurethral resection of the bladder tumor plus intravesical chemotherapy, usually bacillus Calmette-Guérin.

Lymphoid Malignancies

Epidemiology and Risk Factors

Approximately 80,000 new cases of lymphoma were diagnosed in 2019 in the United States. The lifetime risk of developing non-Hodgkin lymphoma is 2.1%, whereas the lifetime risk of developing Hodgkin lymphoma is considerably less. Although incidence has only slightly declined recently, death rates have decreased significantly owing to improvements in treatment. The incidence of non-Hodgkin lymphoma rises with increased age, whereas the incidence of Hodgkin lymphoma shows a bimodal age distribution, with an early peak in the second and third decades of life, then a decline, followed by a sustained increase with older age.

Although most of these cases seem sporadic, familial clustering can be seen, with an increased relative risk in first-degree relatives. Patients with both congenital and acquired immunosuppression (such as HIV infection, organ transplantation, or inherited immunodeficiencies) are at greater risk.

Various viral infections are also associated with increased risk. Epstein-Barr virus is associated with Burkitt lymphoma, seen in African pediatric patients, as well as some cases of Hodgkin lymphoma. Human T-cell lymphotropic virus type 1 is associated with T-cell leukemias and lymphomas, endemic in Japan, West Africa, Central America, the Southeastern United States, and the Caribbean. Hepatitis C virus is associated with an increased risk of lymphoma, particularly splenic marginal zone lymphoma. HIV infection is associated with an increased risk of principally B-cell lymphomas, typically with aggressive histology, more advanced stage, more B symptoms, and a higher risk of extranodal and central nervous system involvement. Kaposi sarcoma herpesvirus (human herpesvirus 8) is associated with primary effusion lymphoma.

Patients with autoimmune rheumatic disorders, such as Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have an increased risk of non-Hodgkin lymphoma.

Evaluation and Diagnosis

Lymphadenopathy is the most common sign of lymphoma. There are many causes of lymphadenopathy, and in most patients, it is of benign origin (infectious or inflammatory). Palpable small cervical and inguinal lymph nodes may be noted in otherwise healthy adults and need not be evaluated further. Increase in size, distribution, and persistence, along with systemic symptoms, raises the concern for lymphoma. CT scan of the chest, abdomen, and pelvis can assess lymph nodes not amenable to physical examination but generally should not be done in asymptomatic patients before establishing the lymphoma diagnosis. An excisional biopsy is often preferable to a core needle biopsy, as it may better determine nodal architecture. Fine-needle aspiration cytology is generally inadequate to make a specific diagnosis. Flow cytometry can suggest monoclonality and demonstrate B-cell or T-cell markers.

Although most patients with lymphoma present with lymph node involvement, presentation in extranodal sites is not uncommon.

KEY POINTS

- Lymphadenopathy is the most common sign of lymphoma.
- Diagnosis of lymphoma is generally established by excision or core needle biopsy, with excision often preferred to better determine nodal architecture.

Classifications, Staging, and Prognosis of Malignant Lymphoma

Diagnosis and classification of lymphoma are established not just on standard cell type and nodal architecture but also on flow cytometry, immunohistochemical stains, and cytogenetic and molecular genetic features. Experienced hematopathologists are essential to obtaining proper classification. However, there can be disagreement among experts and some overlap among tumor types.

Staging the anatomical extent of spread can be simplified through the Ann Arbor staging system (**Figure 3**).

Lymphomas are staged I to IV based on the number of disease sites and the presence of extranodal involvement. Staging involves physical examination, CT scans, and PET scans in most patients. However, PET scans tend to be less sensitive for some very indolent lymphomas (such as small lymphocytic lymphoma and marginal zone lymphomas). The use of PET scans has obviated the need for bone marrow biopsies in many patients with Hodgkin lymphoma and large cell lymphoma, as marrow involvement is rarely found if it is not suggested by PET and abnormal complete blood count.

Lymphoma stages are also designated A or B; A indicates no systemic symptoms are present, and B indicates the presence of one or more of the following: fever >38.0 °C (>100.4 °F), drenching night sweats, or a weight loss of >10% of body weight over the past 6 months.

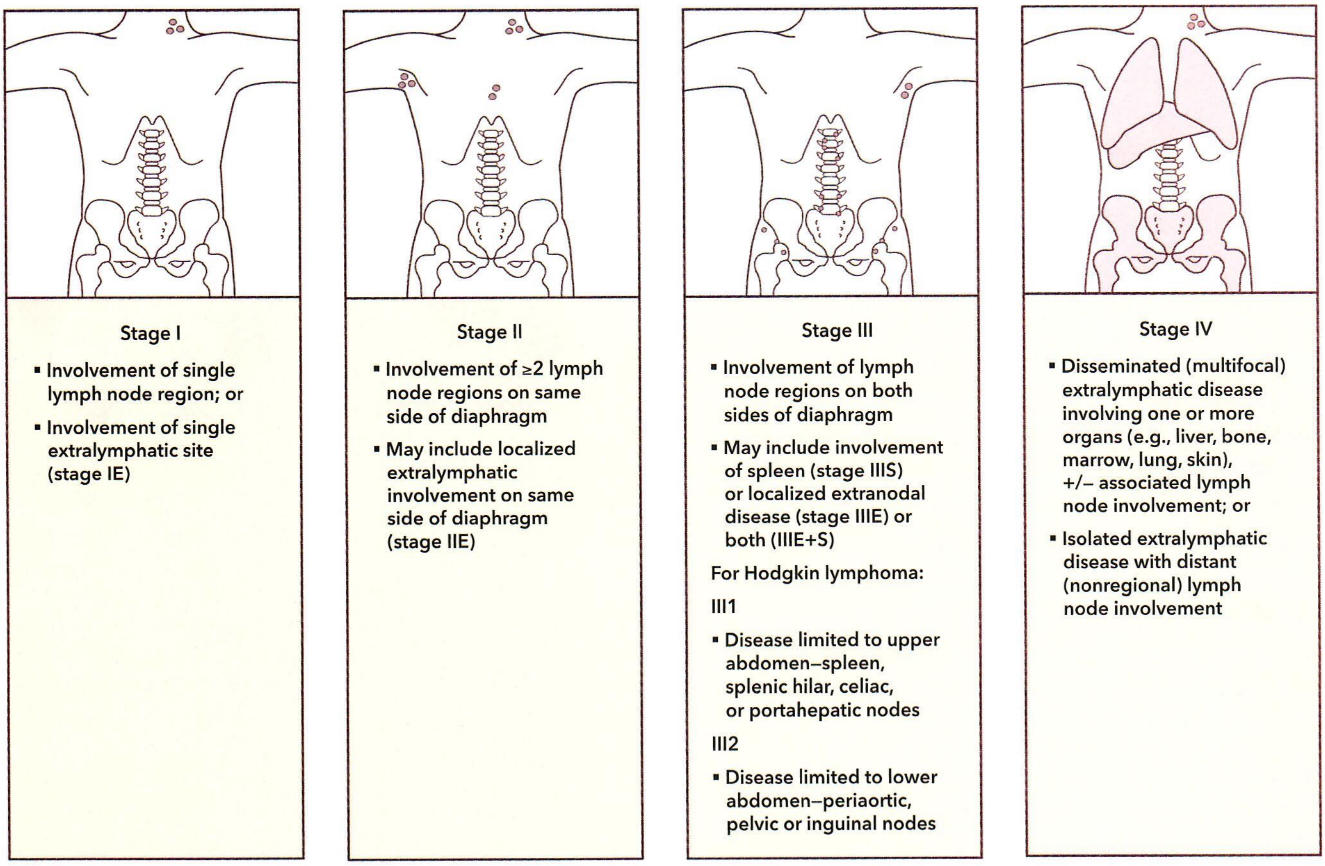
The prognosis of the lymphoma varies greatly depending on the subtype, stage, and comorbidities. Immunophenotypic, cytogenetic, and molecular genetic classifications also commonly inform the prognosis. Prognostic indices have been reported and validated for most common types, including the International Prognostic Index for large cell lymphoma, the Follicular Lymphoma International Prognostic Index, and the Mantle Cell International Prognostic Index.

KEY POINT

- A negative PET scan may obviate the need for bone marrow biopsies in many patients with Hodgkin and large cell lymphoma, but PET scans are less sensitive in the very indolent lymphomas. **HVC**

Non-Hodgkin Lymphomas

Approximately 85% of non-Hodgkin lymphomas are B-cell derived and express surface immunoglobulin and B-cell markers, whereas 15% are T-cell derived.



Stage I

- Involvement of single lymph node region; or
- Involvement of single extralymphatic site (stage IE)

Stage II

- Involvement of ≥2 lymph node regions on same side of diaphragm
- May include localized extralymphatic involvement on same side of diaphragm (stage IIE)

Stage III

- Involvement of lymph node regions on both sides of diaphragm
- May include involvement of spleen (stage IIIS) or localized extranodal disease (stage IIIE) or both (IIIE+S)

For Hodgkin lymphoma:

III1

- Disease limited to upper abdomen–spleen, splenic hilar, celiac, or portahepatic nodes

III2

- Disease limited to lower abdomen–periaortic, pelvic or inguinal nodes

Stage IV

- Disseminated (multifocal) extralymphatic disease involving one or more organs (e.g., liver, bone, marrow, lung, skin), +/– associated lymph node involvement; or
- Isolated extralymphatic disease with distant (nonregional) lymph node involvement

FIGURE 3. Ann Arbor Staging System for Hodgkin and non-Hodgkin lymphoma. Reprinted with permission from Skarkin, A. The Atlas of Diagnostic Oncology, 3rd Edition. Mosby. Copyright Elsevier, 2002.

Indolent B-Cell Lymphomas

The indolent lymphomas may be present for many years without symptoms and typically have a favorable response to various sequential therapies when needed, but all have a tendency for continued relapse.

Follicular Lymphoma

Follicular lymphomas demonstrate lymph node architecture with a follicular morphology. They arise from the germinal center B cells of the lymph node and are characterized by the presence of a t(14;18) translocation that causes an overexpression of the *BCL2* oncogene. Follicular lymphomas are classified based on their dominant cell type: predominantly smaller cells (grade 1), a mixture of smaller and larger cells (grade 2), and predominantly large cells (grade 3). For prognostic and treatment purposes, grades 1 and 2 are commonly combined. Grade 3 follicular lymphoma can be divided into 3A and 3B. Grade 3A follicular lymphoma is more akin in behavior and treatment to grades 1 and 2, whereas 3B is usually treated more like diffuse large B-cell lymphoma.

Follicular lymphoma is the most common indolent B-cell lymphoma and accounts for approximately 30% of non-Hodgkin lymphomas. Many patients are not symptomatic at diagnosis and may not require therapy for many years. Early treatment does not improve outcomes, so asymptomatic patients without bulky disease are usually observed. Some patients may undergo spontaneous, although generally transient, disease regression.

Most patients with follicular lymphoma will present with stage III or IV disease. When therapy is indicated, single-agent rituximab is associated with high response rates and durable remissions. Combining rituximab with chemotherapy (such as the alkylating agent bendamustine or the immune modulator lenalidomide) leads to remission in more than 90% of patients. The use of maintenance rituximab after induction of an initial remission is associated with prolonged duration of remission, but no clear improvement in overall survival. Patients with relapsing or refractory cases can be treated with other approaches, including alternate chemotherapy regimens as well as autologous or allogeneic hematopoietic stem cell transplantation (HSCT).

A minority of patients present with localized disease and can be approached with radiation therapy and/or systemic rituximab-based therapy with curative intent.

Histologic transformation, most typically to a diffuse large B-cell lymphoma, occurs in approximately 30% of patients with follicular lymphomas and is associated with an aggressive course and poor prognosis. Transformation may be suggested by a change in the clinical pattern of disease with new systemic symptoms or rapid progression of a localized area of disease, a rise in serum lactate dehydrogenase, or markedly higher areas of standardized uptake values on PET scans. A new biopsy is required to establish that transformation has occurred.

KEY POINTS

- Many patients with follicular lymphoma are not symptomatic at diagnosis and may not require therapy for many years.
- In advanced-stage follicular lymphoma, rituximab plus chemotherapy or with lenalidomide leads to remission in more than 90% of patients, although the disease will recur in most individuals.
- Histologic transformation of follicular lymphoma to a diffuse large B-cell lymphoma, which should be confirmed by obtaining another lymph node biopsy, is associated with a poor prognosis.

Mucosa-Associated Lymphoid Tissue Lymphoma

Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal marginal zone lymphoma. Gastric MALT lymphoma is associated with *Helicobacter pylori* infection. However, MALT lymphomas can arise in other sites of the gastrointestinal tract as well as in the thyroid, orbits, skin, and lung. They generally demonstrate indolent behavior and a low propensity for transformation. Repetitive immune stimulation, from underlying chronic infection or an autoimmune process, likely plays a role in the pathogenesis of this tumor.

H. pylori–associated gastric MALT lymphoma should be initially treated with antibiotics and proton pump inhibitors, as this treatment may lead to remission. Other localized MALT lymphomas may be treated with irradiation, to which they are quite sensitive. When systemic therapy is required, rituximab alone or in combination with chemotherapy is associated with high response rates.

KEY POINT

- *Helicobacter pylori*–associated gastric mucosa-associated lymphoid tissue (MALT) lymphoma should be treated with antibiotics and proton pump inhibitors initially; other localized MALT lymphomas may be treated with irradiation.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is generally readily diagnosed as an increase in absolute lymphocytes on complete blood count. The lymphocytes are predominantly small and mature appearing, although they may be fragile and form "smudge cells" on the peripheral smear (**Figure 4**). Flow cytometry using peripheral blood is essential in establishing the diagnosis and will reveal B-cell antigens (CD19, 20, and 23), co-expression of CD5 (normally a T-cell marker), and low levels of a monoclonal surface immunoglobulin. Bone marrow aspiration and biopsy are not necessary to diagnose and stage most patients with CLL.

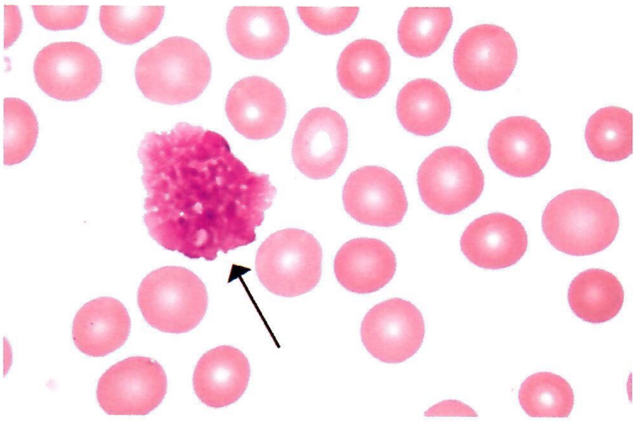


FIGURE 4. The key to suspecting the diagnosis of chronic lymphocytic leukemia is the recognition of an increased blood leukocyte count due to increased numbers of mature lymphocytes and "smudge" cells (lymphocytes that appear flattened or distorted) during the process of preparing the peripheral smear.

Although less common, other lymphomas may appear similar to CLL in peripheral blood smears and must be distinguished by morphology, flow cytometry, and genetic studies. These other disorders include hairy cell leukemia, marginal and mantle zone lymphomas, T-cell lymphoma, and prolymphocytic leukemia.

CLL and small lymphocytic lymphoma represent the same disease, with the designation as leukemia or lymphoma based on the dominant clinical manifestation in either peripheral blood and marrow or nodal involvement, respectively. Both CLL and small lymphocytic lymphoma are treated the same. CLL is now grouped more with the lymphomas than with the leukemias in treatment centers.

CLL is typically an indolent disease, and many patients require no therapy for many years. Prognosis can relate to the extent of cytopenias, organomegaly, and degree of nodal involvement but also on cytogenetic and molecular genetic characteristics.

There have been rapid advances in the number and efficacy of active agents for CLL. Although these therapies are not curative, most patients can now achieve durable remissions once treatment is required. Treatment options include alkylating agents (chlorambucil, cyclophosphamide, bendamustine), purine nucleoside analogues (fludarabine, cladribine, pentostatin), monoclonal antibodies (rituximab, alemtuzumab, ofatumumab, obinutuzumab), and the phosphoinositide-3 kinase inhibitors idelalisib and duvelisib. The Bruton kinase inhibitor ibrutinib is now approved for first-line therapy and active in a broad spectrum of patients, including those with 17p deletion, an indicator of poor prognosis and resistance to older treatments. Venetoclax, an oral *BCL2* inhibitor, is active in first-line and in refractory cases, induces brisk apoptosis, and can induce tumor lysis syndrome. Allogeneic HSCT is rarely performed in those with CLL but has been used in refractory cases in selected, younger patients. Anti-CD19 chimeric antigen receptor T-cell therapy has also been shown to be active in refractory cases.

Patients with CLL are prone to infection, in part related to commonly associated hypogammaglobulinemia. In patients with repeated infections and hypogammaglobulinemia, regular treatment with intravenous gamma globulin reduces infectious events. The infection risk increases in more advanced disease, a result of both impaired T-cell–mediated and B-cell–mediated immune response along with treatment-induced immunosuppression. Patients with CLL and small lymphocytic lymphoma may also develop autoimmune cytopenias such as immune thrombocytopenic purpura and autoimmune hemolytic anemias. Transformation to a large cell lymphoma (Richter transformation) occurs in about 5% of patients with CLL and small lymphocytic lymphoma and is generally associated with a poor prognosis and refractory disease.

KEY POINTS

- Chronic lymphocytic leukemia and small lymphocytic lymphoma are the same disease, but the former predominates in peripheral blood and bone marrow, whereas the latter predominates in lymph nodes.
- The diagnosis of chronic lymphocytic leukemia manifests as an increase in absolute lymphocytes on complete blood count; the lymphocytes are predominantly small and mature appearing and may form “smudge cells” on the peripheral smear.
- Patients with low-stage, asymptomatic chronic lymphocytic leukemia can often be observed without therapy for many years.

Hairy Cell Leukemia

Like CLL, hairy cell leukemia is a low-grade B-cell disorder with characteristic clinical, pathologic, immunophenotypic, and genetic changes. Patients typically present with cytopenias and splenomegaly; lymphadenopathy is typically absent. Circulating “hairy cells,” characterized by cytoplasmic projections, are often identified in the peripheral blood smear (**Figure 5**); when seen on bone marrow biopsy, these cells have a lacunar appearance. Classically, the bone marrow aspirate is a dry tap due to some degree of marrow fibrosis. Flow cytometry is positive for characteristic surface markers. In addition, The *BRAF* V600E mutation has been associated with hairy cell leukemia in most patients and represents not only a diagnostic marker but also a therapeutic target.

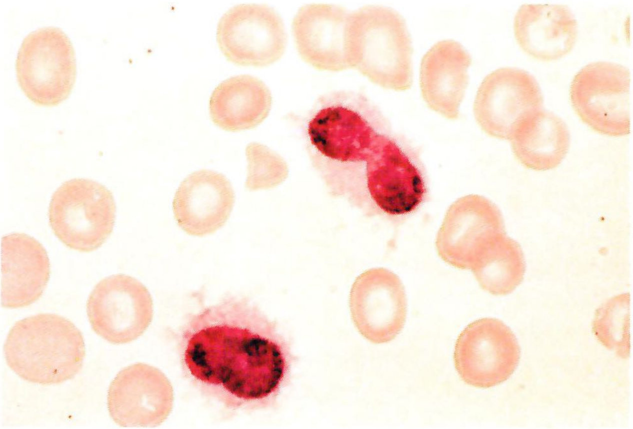


FIGURE 5. Hairy cell leukemia depicted by a peripheral blood smear showing atypical lymphocytes with thread-like cytoplasmic projections from the cell surface.

As with CLL and other low-grade lymphomas, some patients with hairy cell leukemia do not require immediate treatment if not symptomatic. However, the front-line therapy remains purine nucleoside agents, typically pentostatin or cladribine. These agents are highly active, and almost all patients respond, many with durable responses, with only one course of treatment. Relapses can be treated with the alternate purine nucleoside agent, rituximab and the anti-CD22 immunoconjugate moxetumomab pasudotox-tdfk. The selective *BRAF* inhibitor vemurafenib has also shown activity in patients experiencing relapse.

The hairy cell leukemia variant is a distinct entity that typically presents with a high circulating leukocyte count, as opposed to the leukopenia seen in the classic form. These patients respond less well to cladribine and have shorter durations of response.

KEY POINTS

- Patients with hairy cell leukemia typically present with circulating lymphocytes with cytoplasmic projections, termed “hairy cells”; cytopenias; and splenomegaly but no lymphadenopathy.
- Durable remissions of hairy cell leukemia can often be achieved with one course of a purine nucleoside agent such as pentostatin or cladribine.

Aggressive B-Cell Lymphomas

The more aggressive lymphomas, such as diffuse large B-cell and Burkitt lymphoma, are more likely to present with systemic symptoms or signs of rapid tumor progression. These patients have a greater potential for cure with therapy.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma represents approximately 30% of non-Hodgkin lymphomas. These patients often present with symptomatic enlarging lymphadenopathy. Approximately 40% may have symptoms or signs of extranodal disease, and one third have systemic B symptoms. Biopsy specimens show diffuse effacement of normal nodal architecture by large, atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm. Flow cytometry reveals B-cell antigens, and most patients have monoclonal surface immunoglobulin. The B-cell lymphoma 6 (*BCL6*) gene shows rearrangement or other mutations that lead to overexpression in most patients.

Sixty percent of patients have advanced (stage III or IV) disease at diagnosis, and standard therapy is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Consolidative radiation therapy may be given to sites of bulky disease. Residual masses, which are often benign, may remain after treatment. PET may help determine if these represent active disease or just scarring. Patients should also have molecular studies performed to assess for double-hit lymphoma (showing gene rearrangements of MYC in addition to either *BCL2* or *BCL6*), which is associated with worse prognosis. Double-hit lymphoma is usually treated with aggressive chemotherapeutic regimens and up-front autologous HSCT.

Patients with poor prognostic features, such as elevated serum lactate dehydrogenase level, extensive tumor burden, and poor performance status, may receive more aggressive initial therapy, although superiority over standard R-CHOP is unproven. Patients who present with localized disease can be treated with a shorter course of chemotherapy with consolidative radiation therapy. In addition to further standard chemotherapy, autologous HSCT and anti-CD19 chimeric antigen receptor T-cell therapy may be used in patients who relapse.

Primary mediastinal large cell lymphoma is a distinct clinical, morphologic, and genetic lymphoma, often presenting in younger patients. It putatively arises from thymic B cells. It has a female predilection, a tendency to present with bulky but localized disease, and a relatively high cure rate. It may have significant overlap histologically and genetically with nodular sclerosing Hodgkin lymphoma, and some cases may be difficult to classify as one or the other; these are called mediastinal gray-zone lymphomas.

KEY POINTS

- Aggressive B-cell lymphomas, such as diffuse large B-cell lymphoma, progress more quickly than indolent lymphomas but have a greater potential for cure.
- Standard therapy for most patients with advanced-stage diffuse large B-cell lymphoma is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Mantle Cell Lymphoma

Mantle cell lymphomas represent approximately 3% to 6% of non-Hodgkin lymphomas. Median age at diagnosis is 68 years, and there is a 3:1 male predominance. It is defined by a t(11;14) translocation, which leads to constitutive overexpression of cyclin D1, a cell-cycle gene regulator. Patients can present with nodal or extranodal disease, and the disease is usually widely disseminated at diagnosis. Gastrointestinal involvement with lymphomatoid polyposis is well described, as is involvement of the peripheral blood and bone marrow.

Although mantle cell lymphoma is responsive to various conventional chemotherapy regimens and newer agents, it will often relapse. There is no clear consensus on the optimal therapeutic approach, with treatments spanning a spectrum of least aggressive (lenalidomide or bendamustine plus rituximab) to more aggressive (R-CHOP or other aggressive combination regimens with or without HSCT). A subset of patients with indolent disease may not require therapy for many years.

Burkitt Lymphoma

A relatively rare lymphoma, Burkitt lymphoma, is remarkable for its extremely rapid growth. The endemic form occurs primarily in Africa, is a common cause of childhood cancer, and is associated with Epstein-Barr virus infection. Patients may present with a large jaw mass. The sporadic form is more typically seen in the United States, occurs at a somewhat later age, and is more likely to present with abdominal or pelvic involvement. A third variety of Burkitt lymphoma is the immunodeficiency-associated form and occurs in HIV-infected patients. *MYC* gene activation is characteristic of this lymphoma.

Early signs of the tumor lysis syndrome (TLS) are often present in patients with Burkitt lymphoma even before treatment is initiated and should be anticipated during treatment because the tumor is quite chemosensitive. Prophylaxis for TLS should be started before initiation of chemotherapy (for a more complete discussion of TLS, see Oncologic Emergencies and Urgencies). Various aggressive multiagent chemotherapy regimens with rituximab have been associated with high cure rates. These regimens are more intensive than standard lymphoma therapy and are associated with some risk of treatment-related mortality. Treatment of occult central nervous system involvement is included in initial treatment regimens because of the risk for leptomeningeal involvement.

KEY POINT

- Prophylaxis to manage tumor lysis syndrome should be instituted before initiation of chemotherapy for patients with Burkitt lymphoma.

T-Cell Lymphomas

T-cell lymphomas, a heterogeneous group of disorders with distinct clinical features and morphology, represent approximately 10% to 15% of lymphomas in Western countries but are more common in Asia. Diagnosis relies on routine pathology flow cytometry and immunohistochemistry. Monoclonality can be confirmed by findings of clonal rearrangements of the T-cell receptor genes detected by polymerase chain reaction. In general, T-cell lymphomas are more refractory and relapse more quickly in response to therapy than B-cell lymphomas.

Cutaneous T-Cell Lymphoma

Mycosis fungoides and Sézary syndrome are the two major subtypes of cutaneous T-cell lymphoma. The skin findings in mycosis fungoides range from nonspecific macular-papular eruptions or plaques, to more defined skin tumors with ulceration, to diffuse erythroderma (**Figure 6**). There is often a preceding prodromal illness, or "premycotic" period, with milder skin disease that waxes and wanes or that may progress for months or even years with nondiagnostic skin biopsies. Pruritus is common and can be debilitating. Ultimately, as skin involvement becomes more extensive, the disease often progresses to involve extracutaneous sites, including lymph nodes and organs, such as the lung, liver, and gastrointestinal tract. Infections are more common as a function of underlying

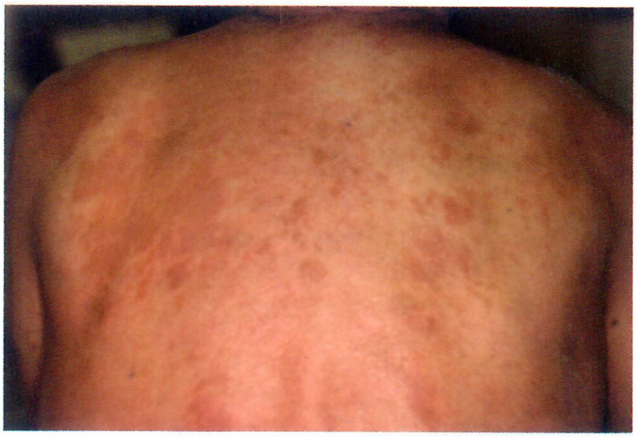


FIGURE 6. Cutaneous T-cell lymphoma (mycosis fungoides) has various presentations, including large patches, plaques, tumors, papules, and generalized erythroderma. The most common presentation consists of large, often pruritic, scaly patches or plaques that vary in size, shape, and color.

immunodeficiency and disruption of the protective barrier provided by healthy skin. Sézary syndrome is a more aggressive form of cutaneous T-cell lymphoma in which diffuse erythroderma characterizes the skin involvement and malignant T cells circulate in the blood.

The staging of cutaneous T-cell lymphoma depends on the extent of skin disease and involvement of lymph nodes and extranodal sites. Early stages of cutaneous T-cell lymphoma are confined to the skin and managed with topical therapy, such as glucocorticoids, retinoids, or ultraviolet light therapy, that may be combined with interferon. Survival is greater than 10 years. More advanced disease is associated with a survival of less than 4 years and requires more aggressive skin treatment with electron beam irradiation and systemic chemotherapy. Patients with Sézary syndrome require systemic chemotherapy. Extracorporeal photopheresis uses psoralens, compounds that enter Sézary cells and sensitize them to injury after activation with ultraviolet light.

Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma, not otherwise specified, is the most commonly diagnosed subtype of peripheral T-cell lymphoma. It typically presents in older adults at an advanced stage, has a male predominance, and has a generally poor clinical outcome compared with B-cell lymphomas.

Various combination chemotherapy regimens have been used. The addition of etoposide or brentuximab vedotin (in patients with CD30-positive tumor cells) to standard combination chemotherapy may provide some benefit as part of initial therapy. The use of chemotherapy designed for acute lymphoblastic leukemia or management with HSCT, both autologous and allogeneic, may benefit some patients, although there is controversy as to when and in whom these are best used. Newer chemotherapy agents such as pralatrexate and romidepsin yield responses in some patients with relapsed disease.

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma can present with nodal as well as extranodal disease, including skin, bone marrow, and bone. Patients commonly have B symptoms. Tumor cells are typically CD30 positive. An important prognostic and potentially therapeutic distinction is the presence or absence of a t(2;5) or variant *ALK* gene translocation and protein expression. Patients diagnosed with *ALK*-positive disease are younger and have a much more favorable prognosis with conventional chemotherapy and may also respond to treatment with crizotinib.

Although still rare, there are increasing reports of anaplastic large cell lymphoma associated with textured breast implants; patients most commonly present with a periprosthetic fluid collection best detected on ultrasound.

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma, initially termed angioimmunoblastic lymphadenopathy, was thought to be a disease of impaired immune regulation rather than a true malignancy; however, patients with this disease are now recognized to have clonal rearrangement of T-cell receptors consistent with a T-cell neoplasm. Patients with angioimmunoblastic T-cell lymphoma often present with systemic B symptoms, generalized lymphadenopathy, hepatosplenomegaly, and a skin rash. They commonly show polyclonal hypergammaglobulinemia and elevated erythrocyte sedimentation rate and C-reactive protein level. Autoimmune manifestations (such as autoimmune hemolytic anemia) may be present. Although the lymphoma in some patients is responsive to glucocorticoids and conventional chemotherapy, it typically has a moderately aggressive clinical course and median survival of less than 2 years.

KEY POINTS

- The skin findings in mycosis fungoides, a subtype of cutaneous T-cell lymphoma, range from nonspecific macular-papular eruptions or plaques, to more defined skin tumors with ulceration, to diffuse erythroderma.
- Sézary syndrome is a more aggressive subtype of cutaneous T-cell lymphoma in which diffuse erythroderma characterizes the skin involvement and malignant T cells circulate in the blood.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma is an aggressive lymphoma that can be of T- or B-cell origin. It is akin to and treated with protocols for acute lymphoblastic leukemia. Presentation with a mediastinal mass, blood or bone marrow, and central nervous system involvement is typical.

Hodgkin Lymphoma

Hodgkin lymphoma represents approximately 10% of lymphomas and is curable in most patients. It most commonly presents in young adults. Presentation with mediastinal, cervical,

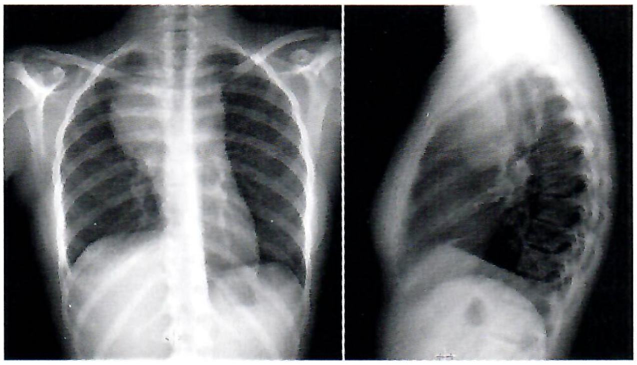


FIGURE 7. Hodgkin lymphoma is the most common lymphoma to involve the mediastinum, shown in this chest radiograph (left) as a mass that originates from the mediastinum, given the convex angles resulting from the mass impinging on the pleura. The lateral film (right) localizes the mass to the anterior mediastinum. Hodgkin lymphoma is the most common cause of anterior mediastinal masses in patients aged 20 to 30 years.

and supraclavicular involvement is particularly common for the nodular sclerosing subtype (**Figure 7** and **Figure 8**). Patients may also present with B symptoms, although that is more commonly seen in elderly patients with more advanced disease. Pruritus may also be a presenting symptom.

Lymph node biopsy specimen shows Reed-Sternberg cells (**Figure 9**), malignant cells that originate from germinal center B cells and are seen in an inflammatory infiltrate. The number of Reed-Sternberg cells and variability in the composition of the infiltrate lead to pathologic subtypes, including nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depleted. Patients are staged by physical examination and PET/CT scan. Staging laparotomies, including diagnostic splenectomy, are no longer done. Routine bone marrow biopsy, in the absence of unexplained blood abnormalities, is not indicated.

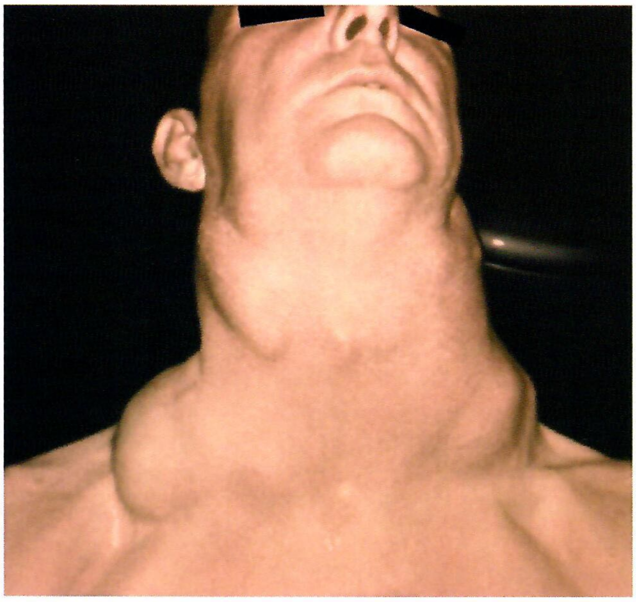


FIGURE 8. This image depicts an anterior view of the head and neck region revealing greatly enlarged cervical lymph nodes, due to Hodgkin lymphoma. Reproduced from CDC Public Image Health Library; image ID 12630.

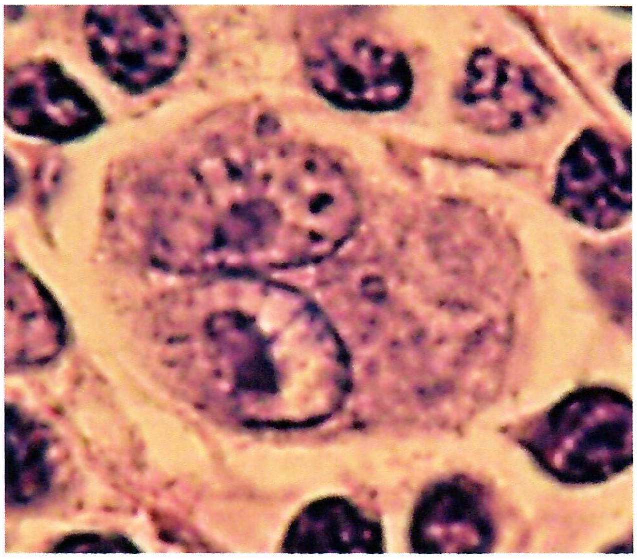


FIGURE 9. Reed-Sternberg cells are large and either are multinucleated or have a bilobed nucleus ("owl's eye" appearance) with prominent eosinophilic inclusion-like nucleoli. They can be seen with light microscopy in biopsies from individuals with Hodgkin lymphoma. They are usually derived from B lymphocytes. When seen against a sea of B cells, they give the tissue a "starry sky" or "moth-eaten" appearance. The absence of Reed-Sternberg cells has very high negative predictive value for Hodgkin disease.

More than 90% of patients present with classic Hodgkin lymphoma pathology and, even with early-stage disease, receive chemotherapy because this has been shown to result in higher cure rates. The doxorubicin, bleomycin, vinblastine, and dacarbazine regimen has been the most commonly used in the United States. Fertility is better preserved and secondary acute leukemia is less common than with prior regimens. For patients with early-stage, favorable disease, treatment can consist of just two courses of chemotherapy and involved site irradiation. Chemotherapy alone for four to six cycles in patients with good response is also an option. For more advanced disease, chemotherapy alone is used. Although the regimen is usually well tolerated, up to 25% of patients may develop bleomycin-induced lung injury during treatment or within 6 months of its conclusion. A newer regimen eliminating bleomycin and substituting brentuximab vedotin (an anti-CD30 monoclonal antibody linked to the anti-tubulin agent monomethyl auristatin E) is associated with less pulmonary toxicity and slightly improved outcomes for patients with advanced disease.

Complete response indicated by PET scan after two to three cycles of chemotherapy is a reliable prognostic indicator. Early repeat PET scan is an appropriate response-adapted strategy in Hodgkin lymphoma and may allow some patients with early-stage disease to forgo radiation therapy and thereby reduce the risks of late irradiation adverse effects.

For patients with relapsed or refractory disease, salvage chemotherapy and autologous or allogeneic HSCT may provide curative options. Brentuximab vedotin is active in refractory disease and has also been used for consolidation after autologous HSCT. The programmed death 1 antibodies (pembrolizumab and nivolumab) are highly active in relapsed or refractory disease.

Nodular lymphocyte-predominant Hodgkin lymphoma is distinct clinically and pathologically from classic Hodgkin lymphoma (nodular sclerosis, mixed cellularity, and lymphocyte depleted). It represents approximately 10% of Hodgkin lymphomas and is more likely to present with localized disease but is associated with a high rate of late relapse. Early-stage disease may be treated with radiation therapy alone. Single-agent rituximab or combined with chemotherapy may be used for more advanced or relapsed disease.

KEY POINTS

HVC
- Physical examination and PET/CT are used to stage patients with Hodgkin lymphoma; laparotomy and splenectomy are no longer performed.
- All patients with classic Hodgkin lymphoma, regardless of stage, receive chemotherapy.
- Complete response indicated by PET scan after two to three cycles of chemotherapy can allow some patients with early-stage classical Hodgkin lymphoma to forgo radiation therapy.

Cancer of Unknown Primary Site

Introduction

Less than 5% of patients with metastatic cancer do not have an identified primary site, with improvements in imaging and other diagnostic techniques steadily decreasing that number. This heterogeneous group of patients is classified as having cancer of unknown primary (CUP).

Diagnosis and Evaluation

On identification of metastatic cancer without a known primary site, a full medical history, physical examination, and a contrast-enhanced CT of the chest, abdomen, and pelvis should be obtained. The most accessible tumor mass should be biopsied, and a limited number of immunohistochemical stains are warranted to assess the nature of the tumor and identify or exclude the most treatable histologies (such as lymphoma or germ cell tumor). Mismatch repair-deficiency, or microsatellite instability, although very rare in CUP, would warrant treatment with immune checkpoint inhibitors. Workup should be focused to diagnose more treatable primaries, histologies, or subtypes of CUP. In addition, specific symptom- or presentation-related evaluations may be pursued, such as upper endoscopy and colonoscopy in patients with gastrointestinal symptoms or evidence of gastrointestinal bleeding. Patients with regional lymphadenopathy require focused evaluation, such as pan-endoscopic evaluation of the head and neck for patients with isolated or dominant cervical lymphadenopathy or anoscopy for those with isolated inguinal lymphadenopathy. In female patients, breast examination and mammography should be done to search for a breast primary cancer, and a gynecologic evaluation should be performed to look for an ovarian primary. Male patients require a testicular examination and, in those with bone metastases, a prostate examination and serum prostate-specific antigen level measurement to evaluate for prostate cancer. Nonspecific tumor markers, such as serum carcinoembryonic antigen, CA-19-9, CA-15-3, or CA-125, are not routinely recommended because they are not definitive for identifying a specific primary site. In some patients, PET scans may suggest the possible primary location, but false-positive results are significant, and PET scan findings are not apt to change the treatment plan. Gene expression arrays have been commercially promoted, but the clinical utility of these tests to identify more effective therapy has not been established, and they should not be used.

Ultimately, CUP is a diagnosis of exclusion after a reasonable evaluation has failed to identify the primary tumor, which either may be too small to be detected or may have been destroyed immunologically and is no longer present. Once the more treatable possibilities have been excluded, specific identification of the site of origin is very unlikely to improve treatment options or clinical outcome. At that point, it should be determined whether the metastatic cancer has a favorable or unfavorable prognosis and if there is a specific, efficacious therapy for that patient.

KEY POINTS

HVC
- In patients with a metastatic cancer of unknown primary site, CT and histologic, endoscopic, and gender-specific cancer evaluations are reasonable; however, nonspecific tumor markers, PET, and gene expression arrays should not be done.
- If reasonable attempts to identify primary cancer have failed, management should shift focus, treating the metastasis based on histology and prognostic factors, as finding the primary site is unlikely to improve treatment options or clinical outcome.

Favorable Prognostic Subgroups of Cancer of Unknown Primary Site

For patients with CUP, the identification of a favorable prognostic subgroup allows selection of specific surgical, irradiation, or chemotherapy to which patients are more likely to respond and on occasion achieves long-term remission and cure.

Poorly Differentiated Cancer of Unknown Primary Site

Poorly differentiated cancers are usually more aggressive than well-differentiated cancers, and metastatic poorly differentiated adenocarcinoma has a poor prognosis; however, some patients with poorly differentiated CUP that is not definitively an adenocarcinoma may have specific treatment options. In particular, young men with predominantly midline poorly differentiated carcinoma, such as those with large retroperitoneal or mediastinal lymphadenopathy, should be carefully evaluated for the possibility of a germ cell tumor. Serum α-fetoprotein and β-human chorionic gonadotropin levels should be measured, and a testicular examination and ultrasonography should be performed. Even if these evaluations have negative findings, an unrecognized germ cell tumor may still exist, and these patients should be treated for this possibility with a platinum-based chemotherapy regimen.

Patients with poorly differentiated neuroendocrine tumors also warrant careful consideration. These tumors frequently both metastasize like small cell lung cancers and respond similarly to platinum-based chemotherapy.

Isolated Regional Lymphadenopathy

Women found to have adenocarcinoma in isolated axillary lymphadenopathy have a more favorable CUP prognosis. These patients should be presumptively considered to have locoregional breast cancer. If mammography is unrevealing, breast MRI should be performed. If the MRI scan is negative, the patient is still assumed to have a presumptive stage II breast cancer. Given the inability to identify the primary, a mastectomy or whole breast radiation therapy is recommended. These patients should all receive adjuvant treatment consistent with a stage II breast cancer diagnosis. Patients with isolated or dominant cervical lymphadenopathy should undergo full endoscopic examination of the upper aerodigestive tract to evaluate for a head and neck primary. Even if a primary is not identified, treatment along a head and neck paradigm with chemotherapy and radiation therapy is often appropriate. In particular, patients with high cervical lymphadenopathy with squamous cell cancer occasionally achieve cure. Supraclavicular lymphadenopathy or adenocarcinoma makes a head and neck primary far less likely, and therapy is less efficacious.

Isolated inguinal lymphadenopathy should prompt anoscopy and careful examination of the perineal and genital regions. Even in the absence of a defined primary tumor, definitive resection or irradiation to inguinal or other isolated solitary or regional lymph nodes may provide long-term tumor control and cures in rare circumstances.

Peritoneal Carcinomatosis in Women

Women who have adenocarcinoma with abdominal carcinomatosis and ascites should be presumptively treated for ovarian cancer, including initial cytoreductive surgery and ovarian cancer chemotherapy regimens.

KEY POINTS

- Patients with cancer of unknown primary who have poorly differentiated carcinoma predominantly in the midline, such as those with large retroperitoneal or mediastinal lymphadenopathy, are likely to have a germ cell tumor and should be treated for that possibility with platinum-based chemotherapy.
- Women with a cancer of unknown primary who have axillary lymphadenopathy and a negative breast MRI scan should be treated for presumptive stage II breast cancer.
- Women with adenocarcinoma with abdominal carcinomatosis and ascites should be treated for presumptive ovarian cancer.
- Patients with isolated or dominant cervical lymphadenopathy and cancer of unknown primary should be treated along a head and neck cancer paradigm with chemotherapy and radiation therapy.

Nonfavorable Subgroups of Cancer of Unknown Primary Site

Therapy for CUP that does not fall into one of the favorable subgroups is empirically directed with chemotherapy and radiation therapy based on the pattern of presentation. CUP presenting above the diaphragm should be evaluated and managed as metastatic lung cancer. CUP that is predominantly below the diaphragm should be managed as gastrointestinal cancer.

Chronic medical comorbidities and patient performance status greatly influence the range of treatment options. As with other solid tumors, patients with several comorbidities and poor performance status are far less likely to benefit from aggressive chemotherapy and are far more likely to experience serious or life-threatening toxicity. Palliative and hospice care should be considered in such patients.

KEY POINTS

- Therapy for cancer of unknown primary that does not fall into one of the favorable subgroups should be managed based on pattern of presentation; cancer presenting above the diaphragm should be treated as metastatic lung cancer, and cancer presenting below the diaphragm should be treated as gastrointestinal cancer.
- Palliative or hospice care is appropriate for patients with an unfavorable subtype of cancer of unknown primary site who have comorbidities and poor performance status. **HVC**

Melanoma

Melanoma has been steadily increasing in incidence worldwide, with risk related to sun exposure. Most melanomas begin in and present with cutaneous disease, but they can also begin in mucosal and ocular sites. About half of cutaneous melanomas arise in preexisting nevi, but many begin in apparently normal skin. Melanoma can also present in nodal or visceral sites without a known cutaneous or mucosal primary. Only 10% of patients with melanoma have a familial history, and mutations in certain genes, such as *CDKN2A*, have been identified in some families. Ocular melanoma is the most common cancer of the eye, and these melanomas have a distinct biology and behavior.

Advances in systemic therapy during the past decade have resulted in significant improvements in survival for patients with metastatic melanoma. These advances include the use of molecular therapy targeted at specific gene mutations and immunotherapy, including the use of immune checkpoint inhibitors.

Treatment of Melanoma

Melanoma has the potential to behave quite aggressively, but it is a highly curable disease when detected and treated early with a wide local excision. For localized melanomas, prognosis is related to the depth of invasion by Breslow depth. A high mitotic rate, lymphovascular invasion, and the presence of ulceration are poor prognostic signs. Surgical resection margins for melanomas do not have to be excessive: 1-cm margins are acceptable for lesions that are less than 1 mm in thickness. Patients with melanomas between 1 mm and 2 mm in thickness should be resected with a 2-cm margin provided that a skin graft is not required for closure. A 1- to 2-cm margin may be selected if wound closure is not feasible without creating a cosmetic deformity or impairing function. Patients with lesions that are greater than 2 mm in thickness should be resected with 2-cm margins. Patients with early-stage disease can be assessed clinically and do not need radiographic staging (for example, CT and PET).

As the depth of invasion increases, the risk of nodal and ultimately distant metastasis increases. Nodal metastases are uncommon in thin melanomas, and nodes are typically not assessed if the melanoma has a Breslow depth of less than 0.8 mm and is without ulceration. Assessing for lymph node metastasis with lymphatic mapping and sentinel lymph node biopsy is often recommended for intermediate and thicker melanomas. Even if the sentinel node is positive, a completion lymph node dissection is no longer routinely performed, as there is no improvement in survival. Patients with positive sentinel lymph node biopsies (stage III) may be followed by clinical examination and serial ultrasounds of the nodal basin involved to detect nodal recurrences. These patients are also eligible for adjuvant systemic treatment.

Systemic therapies for metastatic disease have advanced significantly over the past decade. Conventional cytotoxic chemotherapy has little role in current management. Although interferon and interleukin-2 have some activity in the adjuvant and metastatic setting, respectively, the current focus is on targeted therapy for patients with specific gene mutations and on the use of immune checkpoint inhibitors of programmed cell death transmembrane proteins.

Approximately one half of melanomas harbor a *BRAF* gene mutation (most commonly V600E), and another 20% have an MEK or *NRAS* mutation; all of these mutations activate the mitogen-activated protein kinase pathway. Melanomas with *BRAF* V600E or V600K may respond to oral therapy with the available *BRAF*/MEK inhibitor combinations (dabrafenib/trametinib; vemurafenib/cobimetinib; encorafenib/binimetinib). Combining *BRAF* inhibitors with MEK inhibitors improves the rate and duration of response over *BRAF* inhibitors alone.

In addition to the efficacy of *BRAF* inhibitors, the use of immune checkpoint inhibitors has revolutionized the therapy and prognosis of patients with metastatic melanoma. Cellular immunity is based on T cells recognizing peptide fragments expressed on the surface of antigen-presenting cells when bound to histocompatibility complex molecules. Cytotoxic T-lymphocyte–associated protein 4 is a potent down-regulator of this process. The antibody against cytotoxic T-lymphocyte–associated protein 4, ipilimumab, can result in dramatic tumor response, albeit in a small percentage of patients. Tumor response is independent of *BRAF* status.

Nivolumab and pembrolizumab are both anti–programmed cell death protein 1 antibodies that can result in significant melanoma response rates with sometimes durable response and dramatic survival improvement. Ipilimumab alone has a relatively low response rate (20%) and is associated with considerable toxicity, with various immune-related adverse effects that can include rash, colitis, hepatitis, pneumonitis, myocarditis, and endocrine insufficiency syndromes. Similar adverse effects can occur with nivolumab and pembrolizumab but are less frequent, and these antibodies are associated with a higher response rate (30%-40%). Combining ipilimumab with nivolumab improves response rates compared with either ipilimumab or nivolumab alone but results in significantly more immune-related toxicities. This immunotherapy combination is effective whether or not the patient has *BRAF*-mutated melanoma. Durable benefit in terms of survival is possible in a substantial fraction of patients with metastatic melanoma treated with checkpoint inhibitors.

In addition to their use in metastatic disease, immune checkpoint inhibitors and *BRAF*/MEK inhibitors (in patients with the *BRAF* mutation) have shown survival benefits in the adjuvant setting in patients with resected stage III (nodal) disease.

Although prophylactic lymphadenectomies or completion node dissections for those with positive sentinel nodes have not definitively shown an overall survival benefit, node dissections can be curative in 20% to 50% of patients who present with or develop regional nodal disease. For some patients with distant metastatic disease, surgery may still play a significant role. Melanoma can present with solitary or oligometastatic disease amenable to resection that is curable in some patients. Following metastasectomy, data would support the use of adjuvant systemic therapy to improve overall outcome.

KEY POINTS

- Melanoma is a highly curable disease when detected and treated early with a wide local excision.
- HVC Nodal metastases are uncommon in thin melanomas (Breslow depth less than 0.8 mm) and need not be assessed.
- More than one half of patients have melanoma that harbors a *BRAF* mutation, which may respond to the *BRAF* inhibitors combined with MEK inhibitors.
- The use of immune checkpoint inhibitors has shown significant improvements in survival for patients with regional nodal and metastatic melanoma.

Follow-up

All patients should be encouraged to perform skin self-examinations as well as receive regular skin evaluations by a dermatologist for life every 6 months. Patients with early-stage melanoma need not undergo routine blood testing or imaging studies in the absence of signs or symptoms.

Oncologic Urgencies and Emergencies

Structural Urgencies and Emergencies

Superior Vena Cava Syndrome

Obstruction of the superior vena cava (SVC), or SVC syndrome, is usually caused by malignancies with large mediastinal masses. Lung cancer accounts for almost 75% of cases of SVC syndrome, with lymphoma and metastatic disease each causing approximately 10%; rarer tumors, such as germ cell tumor, thymoma, or mesothelioma, account for the remainder.

Patients typically present with edema of the head, neck, and arms, often with cyanosis, plethora, and distended cutaneous collateral vessels. They may have headache, cough, dyspnea, hoarseness, or syncope. The severity of symptoms depends on the degree of narrowing of the SVC and the speed of onset, with slower development allowing venous collaterals to develop. Most patients do not require emergency intervention, and deaths due to SVC syndrome are rare. A chest CT scan with intravenous contrast usually confirms the diagnosis (**Figure 10**).

Management is based on the severity of symptoms and the underlying malignancy. In patients requiring immediate treatment of respiratory distress, an SVC stent can be placed without tissue diagnosis. For most patients, a tissue diagnosis is obtained, with treatment directed by the type of cancer. Options for obtaining diagnostic tissue include mediastinoscopy, bronchoscopy, thoracentesis (if a pleural effusion is present), or biopsy of a peripheral area of lymphadenopathy. Complication rates of these procedures are usually low.

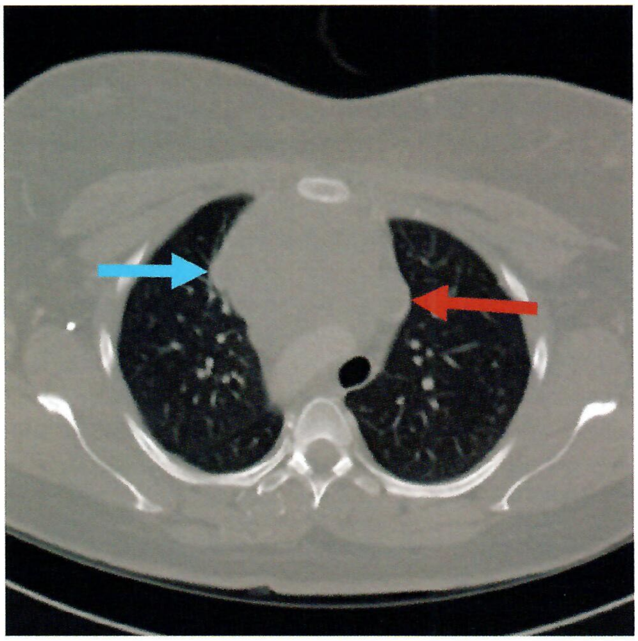


FIGURE 10. Superior vena cava (SVC) syndrome often presents on chest CT scan with bronchial obstruction due to mediastinal mass (*blue arrow*) and SVC compression (*red arrow*).

Cancers that are highly responsive to chemotherapy, such as small cell lung cancer, lymphoma, and germ cell cancers, are treated with initial chemotherapy. Non–small cell lung cancer may be treated with initial chemotherapy, radiation therapy, or both. Initial surgery may be required in thymoma and mesothelioma. Although glucocorticoids and loop diuretics are often used, there is no clear evidence of their effectiveness. If thrombosis is present, anticoagulation should be added.

Treatment of curable malignancies should not be compromised by the presence of SVC syndrome, as prognosis is not otherwise altered.

KEY POINTS

- Most patients with superior vena cava syndrome do not require emergency intervention; a tissue diagnosis should be obtained first with treatment directed by the type of cancer.
- Presentation with superior vena cava syndrome does not worsen prognosis in patients who present with otherwise treatable malignancies.

Venous Thromboembolism

Cancer and cancer treatment are risk factors for venous thromboembolism (deep venous thrombosis and pulmonary embolism). Symptoms such as calf discomfort, pleuritic chest pain, or shortness of breath should prompt evaluation of deep venous thrombosis/ pulmonary embolism (see Hematology).

Central Nervous System Emergencies

Increased Intracranial Pressure

Elevated intracranial pressure can result from primary brain malignancies or from brain metastases, which occur in 10% to 20% of adult patients with cancer. The most common types of primary cancer that cause brain metastases are lung cancer, breast cancer, and melanoma. Median survival after diagnosis of brain metastases varies widely.

Symptoms of increased intracranial pressure include headache, depressed global consciousness, vomiting, and even features of herniation. Emergent CT or MRI imaging will confirm the diagnosis. Glucocorticoids decrease vasogenic edema and relieve symptoms in 75% of patients. Patients with severe symptoms are treated with a loading dose of dexamethasone of 10 to 20 mg followed by 4 to 6 mg every 6 hours. The most critically ill patients may require osmotic diuresis with mannitol, head elevation, hyperventilation, and possibly decompressive surgery. Antiepileptic drugs should be used in the 25% of patients who present with seizures. See Neurology for further discussion of antiepileptic drugs. Anticoagulation can be safely used when indicated. Lumbar puncture is contraindicated in patients with an increased intracranial pressure because of the risk of herniation.

Spinal Cord Compression

Neoplastic epidural spinal cord compression (ESCC) develops in approximately 2.5% of patients with metastatic cancer. The most common types of cancer that cause ESCC in adults are lung, breast, and prostate cancer; myeloma; and lymphoma. Approximately 85% of ESCC cases are due to epidural extension from vertebral body metastases. Lymphomas are more likely to involve a paraspinal mass that extends through the neural foramina to cause cord compression. Pain, often radicular and worse with recumbency, is present in more than 80% of patients and usually precedes neurologic symptoms by several weeks. The absence of neurologic signs should not delay evaluation of such pain. If a sensory level is present, it is typically one to five levels below the actual level of cord compression. Bowel and bladder dysfunction is a late finding that is present in up to half of patients. MRI of the entire thecal sac is the preferred imaging test when ESCC is suspected.

The patient's neurologic status at diagnosis is the most important predictor of outcome. Of patients who are able to walk when starting treatment, 80% remain ambulatory; however, less than 20% of nonambulatory patients regain the ability to walk. Patients are initially treated with glucocorticoids at either a moderate or high dose if paraparesis or paraplegia is present. Definitive treatment with surgery, irradiation, or both depends on whether the patient has a known cancer diagnosis, as well as the stability of the spine, the sensitivity of the cancer to radiation, and the patient's overall prognosis. For patients who are acceptable surgical candidates with an expected survival of at least 3 months, initial decompressive surgery followed by irradiation increases the likelihood of ambulation compared with radiation alone. See Neurology for further discussion of spinal cord compression.

KEY POINTS

- Neoplastic spinal cord compression is initially treated with glucocorticoids; definitive treatment with surgery, irradiation, or both depends on whether the patient has a known cancer diagnosis, the stability of the spine, the sensitivity of the cancer to radiation, and the patient's overall prognosis.
- Neurologic status is the most important predictor of outcome for patients with neoplastic spinal cord compression; ambulatory patients tend to remain ambulatory with treatment, but nonambulatory patients typically do not regain the ability to walk.

Malignant Pleural and Pericardial Effusions

The types of cancer that most commonly cause malignant pleural effusions include carcinomas of the breast, lung, gastrointestinal tract, and ovaries; lymphomas; and mesotheliomas. Patients present with progressive dyspnea and may or may not have concomitant chest pain. See Pulmonary and Critical Care Medicine for further discussion of pleural effusions. Chest radiography is the initial diagnostic study, often followed by CT, which provides more precise anatomic detail. Therapeutic thoracentesis is used as the initial treatment of symptomatic effusions. Further management depends on the rate of reaccumulation, the severity of symptoms, and the patient's prognosis. Recurrent effusion is common, unless the tumor is responsive to systemic therapy. Repeat thoracentesis is appropriate for slowly recurring effusions. For effusions with more rapid reaccumulation, the best options for management are placement of an indwelling pleural catheter with intermittent outpatient drainage or pleurodesis, with similar palliation obtained by either method.

Malignancy accounts for 13% to 23% of pericardial effusions and may be the first presentation of the disease. Lung, breast, and esophageal cancers; melanoma; lymphoma; and leukemia are the most common malignancies that cause pericardial effusions. Cardiac tamponade results when the pericardial fluid pressure impairs filling of one or both ventricles, leading to decreased cardiac output. Patients present with dyspnea, chest discomfort, or fatigue. They usually have elevated jugular venous distention and may have hypotension and peripheral edema. Echocardiography usually establishes the diagnosis. Symptoms from progressive cardiac tamponade may be inappropriately attributed to nonspecific systemic signs of cancer or heart failure until cardiac filling and cardiac output is emergently compromised. See Cardiovascular Medicine for further discussion of cardiac tamponade.

Treatment of symptomatic pericardial effusion involves percutaneous pericardiocentesis or drainage during surgical placement of a pericardial window.

KEY POINT

- For slowly recurring malignant pleural effusions, repeat thoracentesis is appropriate; for more rapidly recurring pleural effusions, either an indwelling pleural catheter with intermittent outpatient drainage or pleurodesis is used.

Metabolic Urgencies and Emergencies

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is caused when tumor cells release their contents into the bloodstream, either spontaneously or as a result of treatment, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These electrolyte abnormalities can lead to acute kidney injury, cardiac arrhythmias, seizures, and death. TLS is seen most often in highly proliferative hematologic malignancies such as acute leukemia and high-grade lymphomas but can develop in other cancers.

The risk of TLS can be categorized based on the volume of cancer mass present; the cell-lysis potential of the cancer; and patient characteristics of preexisting kidney failure, dehydration, acidosis, hypotension, or nephrotoxin exposure. Patients at intermediate risk for TLS can be managed with monitoring of laboratory values, hydration, and allopurinol, and those at high risk should receive intravenous hydration and rasburicase, a urate oxidase enzyme that metabolizes uric acid, before receiving chemotherapy. There is no clear benefit of alkalinization to increase uric acid excretion or prevent uric acid nephropathy, particularly given the availability of rasburicase. Alkalinization increases the risk of hyperphosphatemia and precipitation of calcium phosphate crystals.

Patients who develop TLS require continuous cardiac monitoring; serum measurement of electrolytes, creatinine, and urate every 4 to 6 hours; and correction of electrolyte abnormalities. Depending upon the severity, rasburicase can be given and patients should receive aggressive hydration if kidney function allows, with the use of a loop diuretic if needed to improve urinary output. Patients may require renal replacement therapy for severe oliguria or anuria, persistent hyperkalemia, symptomatic hypocalcemia, or a calcium-phosphate product greater than or equal to 70 mg^2/dL^2.

KEY POINT

- Tumor lysis syndrome should be treated with rasburicase and aggressive hydration if kidney function allows; patients require continuous cardiac monitoring and measurement of electrolyte, creatinine, and urate levels every 4 to 6 hours.

Hypercalcemia of Malignancy

Hypercalcemia of malignancy occurs in 20% to 30% of patients with advanced cancer. It is most frequent in patients with myeloma and cancer of the lung, breast, kidney, and head and neck. Osteolytic bone metastases are usually the cause of hypercalcemia of malignancy in breast cancer and myeloma, although the incidence of hypercalcemia in these patients may be decreasing with the prophylactic use of bisphosphonates. Paraneoplastic production of parathyroid hormone–related protein may occur in localized tumors without widespread bone metastases. Lymphomas and breast cancer can cause hypercalcemia by overproduction of 1,25-dihydroxyvitamin D. Malignancies such as ovarian cancer can produce ectopic parathyroid hormone.

Patients may present with dehydration, acute kidney injury and nausea, vomiting, constipation, fatigue, polyuria, polydipsia, altered mental status, or muscle weakness. Symptoms depend on both the serum calcium level (more severe symptoms with calcium > 14 mg/dL [3.5 mmol/L]) and a rapid rate of rise.

Patients with severe or symptomatic hypercalcemia should receive isotonic saline volume expansion. Loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury. Calcitonin increases kidney excretion of calcium and decreases bone resorption; it can decrease calcium within several hours in responsive patients. Bisphosphonates, such as zoledronic acid, which inhibit bone resorption can lower calcium levels to normal in 50% of patients in 4 days and in 88% of patients in 10 days. The receptor activator of nuclear factor κB ligand denosumab can be considered for patients who do not respond to zoledronic acid. It can be safely used in patients with kidney failure where bisphosphonates may be contraindicated. Effective treatment of the underlying malignancy remains the most appropriate means of controlling hypercalcemia.

KEY POINTS

- Patients with severe or symptomatic hypercalcemia should receive isotonic saline volume expansion; loop diuretics are not recommended unless kidney failure or heart failure is present.
- Calcitonin is recommended for immediate management of symptomatic hypercalcemia and bisphosphonates are preferred to denosumab for longer-term control; treatment of the underlying cancer is the definitive management.

Effects of Cancer Therapy and Survivorship

Effects of Cancer Therapy

Hematologic Toxicity

Myelosuppression remains the major toxicity of many traditional chemotherapeutic agents.

Neutropenia and Fever

Neutropenia typically occurs 5 to 15 days after chemotherapy administration. Serious infectious complications are more likely with increasing severity (absolute neutrophil count below $500/\mu L$ [$0.5 \times 10^9/L$]) and duration of neutropenia. Prompt evaluation is critical and should include assessment for a source and appropriate cultures immediately followed by administration of an empiric, broad-spectrum antibiotic. Antibiotic monotherapy is typically an antipseudomonal β-lactam agent such as cefepime; a carbapenem, such as meropenem; or piperacillin/tazobactam. Other antimicrobials, such as fluoroquinolones, or vancomycin, can be added if antimicrobial resistance is suspected or for management of patients with shock or pneumonia. Specific anaerobic therapy (clindamycin or metronidazole) is not generally needed unless an anaerobic source is suspected. Selected patients without significant comorbidities who are stable and adherent, and in whom a short duration of neutropenia is anticipated, can be treated as an outpatient with intravenous or oral antibiotics. In these patients, guidelines recommend the combination of a fluoroquinolone (i.e., ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate as first-line therapy because this combination is supported by the largest and most convincing body of evidence for safety and effectiveness.

The prophylactic use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor reduces the risk of febrile neutropenia. These medications may be given to patients receiving regimens associated with a high risk of this complication or as secondary prophylaxis in patients with a previous episode of neutropenic fever. Growth factors are not routinely used in the treatment of patients with neutropenic fever but can be considered in those who are at high risk including expected prolonged (> 10 days) and profound ($<0.1 \times 10^9/L$) neutropenia, aged 65 years and older, uncontrolled primary disease, pneumonia, sepsis syndrome, invasive fungal infection, or hospitalization at the time of fever development.

KEY POINTS

- HVC Most patients with neutropenic fever should be managed with monotherapy with an anti-pseudomonal β-lactam agent.
- The prophylactic use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor may be given to patients receiving regimens associated with a high risk of this complication or as secondary prophylaxis in patients with a previous episode of neutropenic fever.
- HVC Growth factors are not routinely used in the treatment of patients with neutropenic fever unless the patient has severe neutropenia ($<100/\mu L$ [$0.1 \times 10^9/L$]) expected to last more than 10 days or has other high-risk features.

Anemia and Thrombocytopenia

Anemia in patients with cancer may be related to chronic inflammation, bone marrow suppression, blood loss, and chemotherapy. Erythrocyte transfusions and erythropoietin administration are sometimes required. Erythropoietin has been associated with more rapid cancer progression and increased risk of venous thromboembolism. This has prompted increased regulation and a significant decrease in the use of erythropoietin therapy in patients with cancer, particularly for those receiving curative or adjuvant treatments.

Thrombocytopenia is generally managed with platelet transfusions, when needed, and appropriate chemotherapy dose reductions and delays (see Hematology).

Nausea and Vomiting

Although nausea and vomiting are common adverse effects of chemotherapy, their incidence and severity have been markedly reduced by antiemetic medications. For patients receiving moderate to severely emetogenic drugs, administration of serotonin receptor antagonists (such as ondansetron or the longer-acting palonosetron) in combination with high-dose glucocorticoid therapy is standard. Neurokinin-1 receptor blockers (such as aprepitant and netupitant) should also be added for those receiving severely emetogenic therapies. The antipsychotic agent olanzapine may also be helpful for reducing emesis. Anticipatory nausea and vomiting may occur in patients who experienced these symptoms during prior chemotherapy cycles. Excellent control of nausea and vomiting during the first few cycles of chemotherapy can prevent anticipatory symptoms. Behavioral therapy or benzodiazepines can be prescribed for patients who experience anticipatory nausea and vomiting.

Dermatologic Effects

Alopecia, although not invariable, is the most common cutaneous adverse effect. Fluoropyrimidines (5-fluorouracil and capecitabine) are associated with palmar-plantar erythrodysesthesia (hand-foot syndrome), characterized as redness, peeling, and tenderness of the palms and soles. Epidermal growth factor receptor inhibitors, such as erlotinib and gefitinib are associated with pustular acneiform eruptions. Monoclonal antibodies against epidermal growth factor receptor (cetuximab and panitumumab) are often associated with more severe acneiform eruption.

Disorders of Pulmonary Function

Bleomycin, nitrosoureas, and gemcitabine may have the strongest associations with pulmonary toxicity, but many other agents have toxicity potential. Additionally, various monoclonal antibodies and targeted therapies can be associated with pulmonary toxicities, including rituximab, trastuzumab, cetuximab, and erlotinib.

Radiation therapy can be associated with pneumonitis, typically occurring within 1 to 3 months of treatment and may lead to the development of radiation fibrosis. See Pulmonary and Critical Care Medicine for further discussion of disorders of pulmonary function related to chemotherapy.

Disorders of Genitourinary and Kidney Function

Cisplatin is the most common chemotherapy affecting kidney function and is associated with acute tubular necrosis. The risk is reduced with the use of aggressive hydration. Both ifosfamide and cyclophosphamide, in high doses, may cause hemorrhagic cystitis. Hemolytic uremic syndrome is most commonly associated with mitomycin and gemcitabine.

Neurologic Toxicity

Peripheral neuropathy is a frequent toxicity of platinum agents, taxanes, vinca alkaloids, and proteasome inhibitors. Oxaliplatin causes a transient hypersensitivity to cold–patients must avoid eating, drinking, or even touching cold items for several days after infusions–as well as a non-temperature-dependent persistent peripheral neuropathy.

Rituximab, along with other immunosuppressive agents, rarely has been associated with progressive multifocal leukoencephalopathy. 5-Fluorouracil and high-dose cytosine arabinoside are associated with cerebellar toxicity. The reversible posterior encephalopathy syndrome has been linked to chemotherapy that targets vascular endothelial growth factor, such as bevacizumab or sunitinib.

Because whole-brain irradiation can cause long-term impairment of cognitive function, focused high-dose irradiation (gamma knife or stereotactic radiosurgery) has become the preferred treatment for patients with limited brain metastases.

Toxicities Related to Immune Dysregulation

With the widespread use of checkpoint inhibitors, patients with cancer are at risk for toxicities associated with the induction of autoimmunity. Antibodies such as ipilimumab; pembrolizumab and nivolumab; and atezolizumab, durvalumab, and avelumab; are associated with immune-related colitis, pneumonitis, hepatitis, dermatitis, endocrinopathies (hypophysitis, thyroiditis, and adrenalitis) and neuritis. These toxicities require prompt recognition, sometimes temporary or permanent cessation of immunotherapy, and often glucocorticoid therapy as well as hormone replacement, if indicated.

KEY POINT

- Standard antiemetic treatment of patients taking severe emetogenic chemotherapy drugs is a serotonin receptor antagonist (ondansetron or palonosetron), a high-dose glucocorticoid, a neurokinin-1 receptor blocker (aprepitant or netupitant), and possibly olanzapine.

Survivorship Issues

Survivorship embodies the care that follows patients on completion of their treatments, including screening for recurrence and secondary malignancies; monitoring for late-organ dysfunction; and helping patients cope with the psychological, sexual, vocational, and other effects of treatment. An initial treatment plan for cancer may be based not only on providing the highest probability of cure but also on a strategy to reduce the risk of long-term complications.

Late Effects of Cancer Therapy

Effects on Bone Health

Bone loss occurs at an increased rate in cancer survivors who have taken long-term glucocorticoids and in women who have undergone surgical, irradiation, or chemotherapy-induced premature menopause or who are taking aromatase inhibitors for breast cancer. Men treated for prostate cancer with androgen deprivation therapy are also at increased risk for osteoporosis. Multiple myeloma may cause generalized bone loss as well as lytic bone disease. Assessment of bone density and treatment or prophylaxis should be considered to reduce the risk of fracture. Treatment commonly includes routine supplements of vitamin D and calcium (while monitoring serum calcium levels) and bisphosphonates or denosumab. Vigilance is required to detect bisphosphonate complications such as osteonecrosis of the jaw (**Figure 11**) and atypical subtrochanteric spiral fractures of the femur.

Disorders of Cardiac Function

Doxorubicin and other anthracyclines can cause irreversible cardiomyopathy; the risk increases with cumulative dosing. Trastuzumab can also induce dose-independent cardiomyopathy that is usually reversible; the risk increases when trastuzumab is combined with anthracyclines. Fluoropyrimidines have been associated with coronary spasm and ischemia during administration.

The tyrosine kinase inhibitors nilotinib and ponatinib are associated with coronary insufficiency, and dasatinib is associated with pulmonary hypertension. The anti–vascular endothelial growth factor antibody bevacizumab is associated with hypertension as well as an increased risk of coronary and other vascular events.

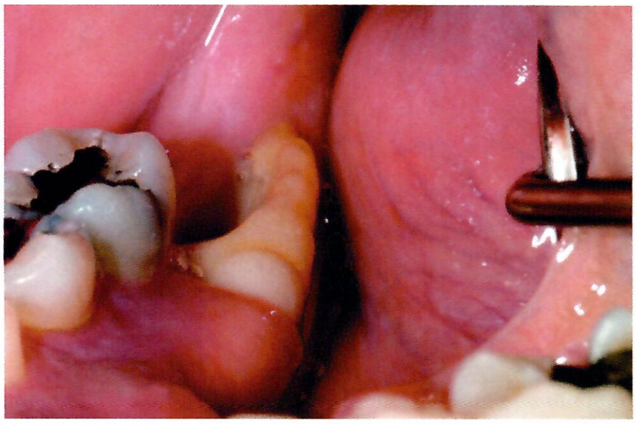


FIGURE 11. Osteonecrosis of the jaw secondary to bisphosphonate therapy.

Monitoring for and management of cardiac complications in cancer survivors is discussed in Cardiovascular Medicine.

Sexual Function and Fertility

Surgery, irradiation, and chemotherapy may all affect sexual function and fertility of both men and women. Altered body image after breast surgery and the generalized fatigue associated with irradiation or chemotherapy may reduce libido. Anxiety and depression further diminish interest in sex. Counseling and support groups may be helpful.

In women, premature menopause and infertility can result from both pelvic radiotherapy and chemotherapy, particularly with alkylating agents. Estrogen is the most effective therapy for vasomotor symptoms related to premature menopause. For women with an intact uterus, estrogen should be combined with progestin. Estrogen replacement therapy is contraindicated in patients with breast and endometrial cancer. Risk factors for infertility relate to the dose and duration of chemotherapy as well as patient age. Consultation with fertility experts should be offered to women who desire future childbearing; egg and embryo harvests may be options. Fertility evaluations can often be done on an emergency basis, so delay in the initiation of definitive cancer treatment is minimized. Men may consider semen cryopreservation.

Tamoxifen, aromatase inhibitors, and ovarian suppression may cause menopausal symptoms, decreased libido, and vaginal dryness. Men commonly experience erectile dysfunction after prostate surgery or irradiation, and androgen deprivation therapy suppresses libido.

Cognitive Decline

Short-term and long-term declines in cognitive function are a complication after cancer therapy. It remains unclear whether cancer and its treatment unmasks preexisting cognitive impairment, whether the decline represents a sign of more rapid aging, or whether there is a more specific neurotoxic effect. Behavioral therapy may be beneficial.

KEY POINTS

- Doxorubicin and other anthracyclines can cause irreversible, dose-related cardiomyopathy; trastuzumab can also induce dose-independent cardiomyopathy that is usually reversible.
- Bevacizumab is associated with hypertension as well as an increased risk of coronary and other vascular events.
- Bone loss occurs in cancer survivors who have taken long-term glucocorticoids; in women who have undergone surgical, irradiation, or chemotherapy-induced premature menopause or who are taking aromatase inhibitors for breast cancer; and in men treated for prostate cancer with androgen deprivation therapy.
- Fertility preservation options should be offered before cancer treatment in patients who desire future childbearing.

Survivorship Care Plan

Providing patients with a prescription for survivorship is an important responsibility of oncologists. At the end of treatment, patients receive a document summarizing their diagnosis, stage, and treatment details, along with recommended follow-up. Recommendations can include surveillance for cancer recurrence, healthy lifestyle modification, and strategy to reduce or prevent the late effects of cancer treatment.

Cancer survivors should, at a minimum, have age- and gender-appropriate cancer screening. Secondary malignancies may develop in cancer survivors owing to a preexisting genetic predisposition, a “field” effect from previous carcinogen exposure, or late effects of previous cancer treatments. Patients with identified genetic mutations with an increased risk of additional malignancies should have genetics counseling. Patients with smoking-related head and neck cancer are prone to second head and neck cancers, as well as lung and esophageal cancers. Patients exposed to chemotherapy with alkylating agents have an increased risk of myelodysplastic syndromes and acute leukemia. Radiation to the neck can be associated with hypothyroidism as well as thyroid cancer years later. Women receiving radiation to the mediastinum for Hodgkin lymphoma and other cancers have a marked increase of breast cancer, particularly if they were treated in adolescence and early adulthood, with the increased risk beginning about 8 years after treatment. Screening MRI, mammography, or a combination of both modalities is recommended for these patients beginning at age 25 years or 8 years after completing radiation therapy, whichever occurs last.

KEY POINTS

- A “prescription for survivorship” provides the patient with recommendations regarding surveillance for cancer recurrence, lifestyle modifications to reduce the risk of a second malignancy, and strategies to prevent or reduce the late effects of cancer treatment.
- Various factors increase the risk of secondary malignancies in patients in remission after therapy for their primary cancer.
- Mediastinal irradiation is associated with a marked increase of breast cancer beginning within 8 years of treatment; screening MRI, mammography, or a combination of both modalities is recommended for women beginning at age 25 years or 8 years after completion of radiation therapy, whichever occurs last.

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Oncology Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates MKSAP 19 Oncology for a maximum of 18 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 18 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Earn Credits or MOC Points Online

To earn CME credits or to apply for MOC points, MKSAP users need to answer at least one of two questions correctly (earning a score of at least 50%) and click the Submit CME button. Each single MKSAP 19 self-assessment question qualifies for one quarter of a CME credit hour or ABIM MOC point.

MKSAP 19 Subscribers can enter their self-assessment question answers and submit for CME/MOC in two ways:

1. Users of MKSAP 19 Complete who prefer to use their print books and a paper answer sheet to study and record their answers can use the printed answer sheet at the back of this book to record their answers. The corresponding online answer sheets, which are available on the MKSAP 19 Resource Page, may be used to transcribe answers onto the online answer sheets. Users may then submit their answers to qualify for CME credits or MOC points (see below for information on Opting in for MOC). Users who prefer to record their answers on a paper answer sheet should save their answer sheet for future use. Users who study with MKSAP 19 print can also submit their answers directly within MKSAP 19 Digital by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions.
2. Users of MKSAP 19 Digital can enter their answers within the digital program by accessing the self-assessment questions dashboard and selecting the preferred subspecialty section to begin answering questions and clicking the Submit CME button once they qualify for CME and are ready to submit. Learners should keep in mind their yearly CME and MOC deadlines when determining the appropriate time to submit.

Learners' CME/MOC submission progress will be shown on the MKSAP 19 Digital CME/MOC/CPD page.

Opting in for MOC

MKSAP 19 users can opt in for simultaneous submission of CME and MOC points as they answer self-assessment questions. To opt in, users will be required to complete a form requesting their name, date of birth, and ABIM number. The MOC Opt-in Form will be presented upon the user's first CME submission and needs to be completed only once.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 58-year-old woman is evaluated for a 6-week history of fatigue, anorexia, and abdominal distention. She has lost 2.3 kg (5 lb) over the past week. For the past 4 days, she has been so debilitated that she has difficulty ambulating due to abdominal pain and fatigue; she has been bedbound for the past 48 hours. Prior to this, she had been working full time and running approximately 12 miles per week. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals distention with normal bowel sounds. The liver edge is palpable 4 cm below the right costal margin. Stool sample is guaiac-positive.

Laboratory studies:

Hemoglobin	9.7 g/dL (97 g/L)
Bilirubin	2.3 mg/dL (39.3 µmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)

Contrast-enhanced CT scan demonstrates a mass in the descending colon and hepatomegaly with multiple metastatic lesions. A colonoscopy identifies a mass in the left colon, and a biopsy shows adenocarcinoma.

Which of the following is the most appropriate management?

(A) Fluorouracil
(B) Fluorouracil and oxaliplatin
(C) Hemicolectomy
(D) Supportive, comfort-oriented care

Item 2

A 65-year-old man is evaluated for a single episode of painless gross hematuria that occurred 1 month ago. Medical history is notable only for atrial fibrillation managed with metoprolol and rivaroxaban.

On physical examination, vital signs are normal. Cardiac examination reveals an irregularly irregular rhythm.

Urinalysis is normal.

Ultrasound of the kidneys and bladder is normal.

Which of the following is the most appropriate management?

(A) Cystoscopy
(B) Repeat urinalysis in 1 week
(C) Substitute warfarin for rivaroxaban
(D) Urine cytology
(E) Reassurance and no additional intervention

Item 3

A 52-year-old woman is evaluated in the office for a left breast lump that developed 3 months ago. She is asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, there is a 1.8-cm firm mass in the upper outer left breast. There is no axillary or supraclavicular adenopathy.

Complete blood count and comprehensive metabolic profile, including alkaline phosphatase level, are normal.

Mammogram and ultrasound confirm a 1.8-cm mass in the left upper outer breast.

Core biopsy of the left breast reveals estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor receptor 2–negative invasive ductal carcinoma.

Which of the following is the most appropriate pretreatment imaging for this patient?

(A) Chest radiograph and bone scan
(B) CT of the chest, abdomen, and pelvis
(C) CT of the chest, abdomen, and pelvis and MRI of the brain
(D) No imaging

Item 4

A 62-year-old man is evaluated for adjuvant therapy after surgical removal of an adenocarcinoma of the colon. Postsurgical pathology revealed a tumor penetrating the full thickness of the colonic wall, and cancer is found in three of 17 lymph nodes. Presurgical imaging revealed no evidence of distant metastatic disease.

Which of the following is the most appropriate adjuvant treatment?

(A) Bevacizumab
(B) Capecitabine
(C) Oxaliplatin, fluorouracil, and leucovorin (FOLFOX)
(D) Radiation therapy
(E) No additional therapy

Item 5

A 68-year-old man is evaluated for early satiety and right upper quadrant discomfort. He is otherwise well. He reports that he is still working full time and walks about a half mile to and from work each day.

On physical examination, vital signs are normal. Examination is notable for hepatomegaly.

Complete blood count is normal. On serum chemistry testing, alkaline phosphatase and aminotransferase levels are elevated; bilirubin and creatinine levels are normal.

CT scan of the chest, abdomen, and pelvis shows hepatomegaly with multiple metastatic lesions and abdominal carcinomatosis with a small amount of ascites. No other abnormalities are noted. Liver biopsy reveals adenocarcinoma.

The patient is diagnosed with metastatic cancer from an unknown primary.

Which of the following is the most appropriate management?

(A) Measure serum CA-19-9, CA-15-3, and CA-125 antigens
(B) Obtain a gene expression array
(C) PET
(D) Upper endoscopy, wireless capsule endoscopy, and colonoscopy
(E) No additional testing; initiate combination chemotherapy

Item 6

A 52-year-old man is seen following an axillary lymph node biopsy confirming a diagnosis of large B-cell lymphoma.

Complete blood count, liver chemistry tests, and electrolyte, blood urea nitrogen, and creatinine levels are normal.

PET/CT shows uptake in left axillary, mediastinal, hilar, and retroperitoneal nodes, as well as multiple foci in the ileum, ribs, and vertebral bodies.

Which of the following is the most appropriate staging test to perform next?

(A) Bone marrow biopsy
(B) Brain MRI
(C) CT-guided biopsy of retroperitoneal lymph node
(D) Serum lactate dehydrogenase measurement

Item 7

A 54-year-old woman is evaluated for a several-month history of increasing abdominal girth. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals ascites. Pelvic examination and the remainder of the physical examination are normal.

Complete blood count and comprehensive metabolic profile are normal.

Contrast-enhanced CT scan of the chest, abdomen, and pelvis reveals ascites with areas of peritoneal and omental thickening consistent with metastatic cancer. No abnormalities of the liver are noted, and the adnexa appear normal.

Paracentesis is performed, and cytology reveals adenocarcinoma.

Surgical debulking of the peritoneal tumor is planned.

Which of the following is the most appropriate adjuvant management?

(A) Chemotherapy with a gastrointestinal cancer regimen
(B) Chemotherapy with ovarian cancer regimen
(C) Immunotherapy with a programmed death receptor 1 inhibitor
(D) Total abdominal irradiation

Item 8

A 45-year-old woman is evaluated after experiencing lower pelvic pain and heavy vaginal bleeding.

On physical examination, vital signs are normal. Pelvic examination reveals a bulky and friable cervical mass with extension to the lower third of the vagina. The remainder of the examination is normal.

Biopsy of the cervical mass reveals squamous cell carcinoma. CT scan of the abdomen and pelvis reveals a large cervical mass with extension to the pelvic sidewall and pelvic adenopathy.

Which of the following is the most appropriate treatment for this patient?

(A) Concurrent radiation therapy and cisplatin
(B) Hysterectomy and pelvic node dissection
(C) Radiation therapy
(D) Radiation therapy and pembrolizumab

Item 9

H

A 64-year-old man is evaluated in the emergency department for 5 days of increasing bouts of diarrhea. He was diagnosed with metastatic melanoma 2 months ago and has received three doses of immunotherapy with ipilimumab and nivolumab. He was seen 3 days ago for diarrhea (two loose stools daily). Evaluation for infectious causes of diarrhea, including *Clostridioides difficile*, was initiated, and loperamide was begun. Today he reports increased diarrhea, with up to five loose stools per day. He takes no additional medications.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 95/70 mm Hg, and pulse rate is 100/min. Abdomen is slightly tender and distended without hepatosplenomegaly.

Complete blood count, metabolic panel, and thyroid-stimulating hormone level are normal, and stool studies, including nucleic acid amplification testing for *Clostridioides difficile* toxin genes, are negative. Fecal calprotectin and fecal lactoferrin levels are elevated.

Ipilimumab and nivolumab are discontinued. The patient is admitted to the hospital for intravenous fluids and additional treatment.

Which of the following is the most appropriate additional treatment?

(A) Budesonide
(B) Infliximab
(C) Mesalamine
(D) Methylprednisolone

Item 10

A 79-year-old man is evaluated in the office following a recent hospitalization for pneumonia. This is his second episode of pneumonia in the past year. Medical history is notable for chronic lymphocytic leukemia. His disease course has been followed without treatment for the past 9 years.

On physical examination, vital signs are normal. Pulmonary examination is normal. There is diffuse adenopathy and splenomegaly.

Laboratory studies:

Leukocyte count	46,000/µL (46×10^9/L) with 92% lymphocytes, 6% neutrophils, 1% bands, and 1% monocytes
IgG	320 mg/dL (3.2 g/L)
IgA	20 mg/dL (0.2 g/L)
IgM	34 mg/dL (0.34 g/L)

Which of the following is the most appropriate treatment for this patient?

(A) Granulocyte-colony stimulating factor
(B) Ibrutinib
(C) Intravenous gamma globulin
(D) Splenectomy

Item 11

A 25-year-old man is evaluated for a 2-week history of an enlarging mass in the left testicle. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There is a 3-cm, hard, left testicular mass on examination.

Results of laboratory studies show an α-fetoprotein level of 2500 ng/mL (2500 µg/L) and a β-human chorionic gonadotropin level of 5120 IU.

Ultrasound reveals a solid mass in the left testicle. CT of the abdomen and pelvis reveals no enlargement of retroperitoneal nodes or other abnormalities. Chest radiograph is normal.

Which of the following is the most appropriate management?

(A) Chemotherapy
(B) Needle biopsy of the testicular mass
(C) PET/CT
(D) Radical inguinal orchiectomy

Item 12

A 63-year-old woman is evaluated for a mass in her right axilla. She first noticed the mass 2 months ago. She has also had a persistent cough. She was diagnosed 3 years ago with stage IIB right breast cancer for which she underwent lumpectomy, chemotherapy, and breast irradiation.

On physical examination, vital signs are normal. There is a firm, fixed, 2-cm mass in the right axilla. Bilateral breast examination reveals no masses or nodules. The remainder of the examination is normal.

Chest radiograph shows multiple bilateral pulmonary nodules. CT scan of the chest, abdomen, and pelvis shows new right axillary adenopathy and multiple peripheral pulmonary nodules measuring up to 1.5 cm in size. There is no hilar or mediastinal adenopathy.

Which of the following is the most appropriate management?

(A) Biopsy pulmonary nodule
(B) Biopsy right axillary mass
(C) Initiate chemotherapy
(D) Initiate endocrine-based therapy

Item 13

A 71-year-old woman is evaluated for metastatic colon cancer. Stage III colon cancer was diagnosed and treated with surgery and adjuvant chemotherapy 3 years ago. The tumor was found to be mismatch repair–deficient. Evaluation for a germline mismatch repair protein deficiency (Lynch syndrome) was negative. Six months ago, she was found to have numerous hepatic metastases and involvement of multiple retroperitoneal lymph nodes. She was treated with a standard chemotherapy regimen and was stable for 4 months. Current CT imaging shows tumor growth in the liver and retroperitoneal lymph nodes. The patient remains asymptomatic with good performance status.

On physical examination, vital signs and other examination findings are normal.

The patient's carcinoembryonic antigen level has increased to 33.5 µg/L (normal, <5.0 µg/L).

Which of the following is the most appropriate management?

(A) Comfort-oriented care and hospice management
(B) Programmed death receptor 1 inhibitor
(C) Stereotactic radiation therapy
(D) Tyrosine kinase inhibitor

Item 14

A 62-year-old woman was diagnosed 2.5 years ago with left-sided, stage IIB, estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer treated with mastectomy, postmastectomy irradiation, and letrozole, which was started 2 years ago. Medical history is otherwise unremarkable. Current medications are letrozole, a calcium supplement, and cholecalciferol.

Which of the following is the most appropriate screening or surveillance test to perform at this time?

(A) CT of chest, abdomen, and pelvis
(B) Dual-energy x-ray absorptiometry
(C) Echocardiogram
(D) Pelvic ultrasound

Item 15

A 62-year-old woman undergoes follow-up evaluation for epithelial ovarian cancer. Seven months ago, she underwent surgical debulking with optimal cytoreduction, and the primary tumor and visible metastases were all resected. Surgery was followed by platinum-taxane chemotherapy. There has been no evidence of disease recurrence. Germline genetic testing revealed a *BRCA1* mutation. Her medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is a well-healed laparotomy incision.

Which of the following is the most appropriate additional treatment for this patient?

(A) Irradiation
(B) Poly (ADP-ribose) polymerase inhibitor therapy
(C) Second course of chemotherapy
(D) No additional treatment

Item 16

A 37-year-old woman is evaluated 6 years after completing treatment for breast cancer. She has a history of stage II estrogen receptor–positive/human epidermal growth factor receptor 2–positive breast cancer. She underwent lumpectomy; irradiation; chemotherapy with doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; and then completed 5 years of tamoxifen. She and her partner now want to have a child.

Which of the following risks will be increased with pregnancy?

(A) Breast cancer recurrence
(B) Breast cancer-related mortality
(C) Congenital malformations in offspring
(D) No increase in congenital malformations or breast cancer risk

Item 17

A 55-year-old woman is evaluated in the office following a recent diagnosis of metastatic adenocarcinoma of the lung. She has excellent performance status. Medical history is otherwise unremarkable, and she takes no medications.

There are no molecular alterations (epidermal growth factor receptor, *ALK*, *ROS1*). Programmed death ligand-1 expression is negative.

Which of the following is the most appropriate treatment?

(A) Combination chemotherapy
(B) Combination chemotherapy plus pembrolizumab
(C) Pembrolizumab monotherapy
(D) Single-agent chemotherapy

Item 18

A 56-year-old man is evaluated for an enlarging, painful inguinal lymph node he first noticed 1 month ago. He has a history of follicular lymphoma of 8 years' duration. The patient was treated in the past with two courses of rituximab 8 and 3 years ago with durable partial responses. For the past 3 years, he had stable diffuse adenopathy managed with observation. He has no other symptoms.

On physical examination, vital signs are normal. The patient has diffuse adenopathy in the neck, axillae, and right inguinal area and a new left inguinal conglomerate nodal mass measuring 5 × 7 cm.

Complete blood count and metabolic profile are normal.

PET/CT scan shows diffuse uptake in axillary, mediastinal, hilar, and mesenteric nodes with elevated standardized uptake values in the 4 to 12 range, but 28 in the left inguinal area.

Which of the following is the most appropriate management?

(A) Begin bendamustine and rituximab
(B) Begin rituximab
(C) Biopsy of the left inguinal nodes
(D) Radiation therapy to the left inguinal nodes

Item 19

A 41-year-old woman is evaluated for a 3-month history of depressed mood nearly every day, low energy, loss of interest in nearly all activities, fatigue, and poor concentration. Medical history is significant for stage II, estrogen receptor–positive, human epidermal growth factor 2–negative breast cancer diagnosed 2 years ago. Her only medication is tamoxifen.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Complete blood count, comprehensive metabolic panel, and thyroid-stimulating hormone level are all normal.

Which of the following is the most appropriate treatment?

(A) Discontinue tamoxifen
(B) Prescribe bupropion
(C) Prescribe fluoxetine
(D) Prescribe venlafaxine

Item 20

A 56-year-old woman is evaluated for findings suspicious for inflammatory breast cancer.

On physical examination, vital signs are normal. The right breast is enlarged, and the skin is thickened and erythematous. There is a 5- × 4-cm mass in the lower outer breast. There is an enlarged right axillary node.

Right breast mammogram reveals a mass in the lower outer breast with calcifications that span approximately 5 cm in size. Right axillary ultrasound reveals an enlarged axillary lymph node. Core biopsy of the breast reveals estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor 2–negative invasive ductal carcinoma. CT of the chest, abdomen, and pelvis and bone scan show no evidence of distant metastatic disease.

Which of the following is the most appropriate sequence of therapies for this patient?

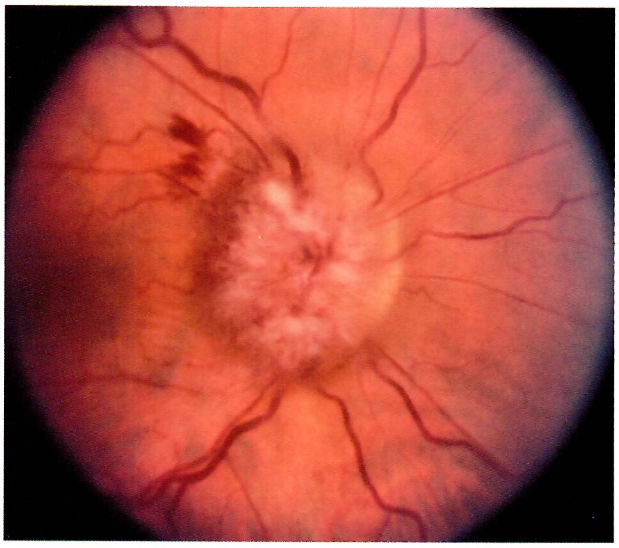
(A) Mastectomy, chemotherapy, irradiation
(B) Preoperative chemotherapy, lumpectomy, irradiation
(C) Preoperative chemotherapy, mastectomy, irradiation
(D) Irradiation, mastectomy, chemotherapy

Item 21

A 45-year-old woman is evaluated for headaches and nausea that started 2 weeks ago. Her headaches are worse in the morning and have been associated with vomiting.

Medical history is significant for metastatic breast cancer diagnosed 4 years ago. She is currently receiving treatment with capecitabine and trastuzumab. Additional medications are ondansetron and prochlorperazine.

On physical examination, vital signs are normal. Funduscopic examination findings are shown.



MRI of the brain reveals a 4-cm rim-enhancing lesion in the left frontal lobe with surrounding vasogenic edema. There is no midline shift or evidence of herniation.

Which of the following is the most appropriate initial treatment?

(A) Dexamethasone
(B) Stereotactic radiation therapy
(C) Surgical resection
(D) Whole brain radiation therapy

Item 22

A 49-year-old woman is evaluated for pain and bright red blood with bowel movements for the past 6 weeks.

Physical examination is notable only for a hard mass palpable on rectal examination in the anal canal. Biopsy reveals squamous cell carcinoma.

Pelvic MRI confirms a 4-cm anorectal mass. No enlarged lymph nodes are noted. Contrast-enhanced CT scan of the chest and abdomen is normal.

Which of the following is the most appropriate treatment?

(A) Immunotherapy with programmed death receptor 1 inhibitor
(B) Irradiation
(C) Irradiation with concurrent chemotherapy
(D) Surgical resection

Item 23

A 65-year-old man is evaluated after being diagnosed with high-risk prostate cancer. He is asymptomatic. Transrectal ultrasound biopsy showed multiple foci of prostate cancer in both lobes with the highest Gleason score of 8.

On physical examination, vital signs and the remainder of the examination are normal.

CT and bone scan are negative for metastatic disease.

The patient has been started on treatment with androgen deprivation therapy plus radiation therapy.

Which of the following is the most appropriate screening test to perform next?

(A) Dementia screening
(B) Doppler ultrasonography of the lower extremities
(C) Dual-energy x-ray absorptiometry scan
(D) Exercise stress test

Item 24

A 45-year-old man is evaluated following a recent diagnosis of a gastrointestinal neuroendocrine tumor. The tumor was discovered after an abdominal CT scan for acute alcohol-related pancreatitis. The CT scan revealed more than 12 hypodense lesions in the liver ranging in size from 0.5 cm to 2.5 cm (replacing approximately 5% to 10% of the liver volume) and a 2-cm mesenteric mass. Following recovery from the pancreatitis, a core needle biopsy of one of the liver lesions was obtained and revealed a well-differentiated, low-grade neuroendocrine tumor. The patient reports feeling well since discharge from the hospital. He is enrolled in a 12-step facilitation program for alcohol use disorder.

On physical examination, vital signs are normal. The remainder of the examination is normal.

Which of the following is the most appropriate next step in management?

(A) Expectant observation
(B) Hepatic artery embolization
(C) Peptide-receptor radiotherapy with radiolabeled somatostatin analogue
(D) Resection of the mesenteric mass

Item 25

H

A 63-year-old woman is evaluated in the hospital following successful treatment of severe hypercalcemia with intravenous fluids and zoledronic acid. She was subsequently diagnosed with widely metastatic, poorly differentiated adenocarcinoma of the lung. No tumor molecular alterations were noted. She has experienced a 30-pound weight loss over the past 7 months. She has been unable to independently perform activities of daily living for the past 4 months. She reports no significant difficulty with pain.

On physical examination, vital signs are normal. BMI is 19. She is cachectic and frail-appearing. Pulmonary examination reveals decreased breath sounds in the right lung base. The patient is unable to transfer out of bed or walk without assistance.

CONT.

Which of the following is the most appropriate management?

(A) Chemotherapy plus bevacizumab
(B) Combination chemotherapy
(C) Radiation therapy
(D) Supportive care/hospice

Item 26

A 55-year-old woman is admitted to the hospital for chemotherapy following a diagnosis of Burkitt lymphoma. She is considered to be at high risk for tumor lysis syndrome.

On physical examination, blood pressure is 110/60 mm Hg and pulse rate is 110/min; the remainder of her vital signs are normal. The patient has large, palpable, bilateral cervical, supraclavicular, and axillary lymphadenopathy. Cardiopulmonary examination is normal.

CT imaging of the chest, abdomen, and pelvis at the time of diagnosis revealed bulky mediastinal and periaortic lymphadenopathy.

Intravenous isotonic saline is administered at 200 mL/hour.

Which of the following is the most appropriate additional preventive therapy?

(A) Acetazolamide
(B) Allopurinol
(C) Furosemide
(D) Rasburicase

Item 27

A 59-year-old man is evaluated for a 2-month history of worsening dry cough. He has no other symptoms. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal, and all other physical examination findings are unremarkable.

CT scan of the chest reveals a 2.1-cm right middle lobe mass and adjacent hilar adenopathy. PET/CT scan with fluorodeoxyglucose uptake in the known mass and hilar nodes is otherwise negative.

Pathology at surgery reveals a 2.5-cm squamous cell carcinoma with negative margins, two positive hilar nodes, and no positive mediastinal nodes.

Brain MRI scan is negative for metastatic disease.

Which of the following is the most appropriate treatment?

(A) Cisplatin-based chemotherapy
(B) Combined cisplatin-based chemotherapy and irradiation
(C) Erlotinib
(D) Prophylactic cranial irradiation

Item 28

A 65-year-old woman is evaluated for a lung nodule found on a preoperative chest radiograph for upcoming elective surgery. Medical history is significant for a malignant melanoma that was resected from the right chest wall 4 years ago. A right axillary sentinel lymph node was negative at that time. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is a healed incision site from prior right chest wall melanoma resection. There is no evidence of local or in-transit recurrence and no axillary or other adenopathy.

PET/CT scan shows uptake in the right lung nodule but no other evidence of disease. CT-guided biopsy of the right lung lesion shows *BRAF* V600E–mutated malignant melanoma.

Which of the following is the most appropriate initial treatment for this patient?

(A) *BRAF* inhibitor
(B) *BRAF* inhibitor and a MEK inhibitor
(C) Immunotherapy
(D) Surgical resection

Item 29

A 32-year-old woman is evaluated after being diagnosed with estrogen receptor–positive breast cancer. The planned treatment strategy includes surgery, chemotherapy with docetaxel and cyclophosphamide, and 5 years of endocrine therapy. She is interested in having children in the future. Medical history is otherwise unremarkable.

Which of the following is most likely to result in a subsequent pregnancy?

(A) Attempt conception during endocrine therapy
(B) Attempt conception after endocrine therapy
(C) Depot leuprolide
(D) Embryo/oocyte cryopreservation

Item 30

A 51-year-old man is evaluated following biopsy of the prostate gland. His father died of prostate cancer at the age of 60 years, and his mother was diagnosed with breast cancer at the age of 45 years.

Biopsy of the prostate revealed adenocarcinoma with bilateral gland involvement; his Gleason score was 9. Bone scan confirmed multiple osseous metastatic lesions.

Which of the following is the most appropriate management?

(A) Cystoscopy
(B) PET/CT
(C) Prostate-specific antigen density measurement
(D) Referral to a genetic counselor

Item 31

A 37-year-old woman is evaluated during a routine examination. Medical history is significant for Hodgkin lymphoma, diagnosed at age 29 years and treated with combination chemotherapy and mantle irradiation. There have been no recurrences of the Hodgkin lymphoma. Two years ago, she developed hypothyroidism. Her only medication is levothyroxine.

On physical examination, vital signs are normal. There are no breast masses or nodules and no axillary adenopathy. The remainder of the examination is normal.

Which of the following screening tests should be done now?

(A) Mammography
(B) Mammography and MRI of the breast
(C) MRI of the breast
(D) Ultrasonography of the breast

Item 32

A 74-year-old woman is evaluated for cough and dyspnea on exertion, which has progressed over the past 6 months. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There are scattered crackles throughout the left chest. There is no adenopathy.

CT scan of the chest, abdomen, and pelvis shows only patchy, nodular infiltrates in the left upper and left lower lobes of the lung.

Transbronchial lung biopsy shows non-Hodgkin, mucosa-associated lymphoid tissue lymphoma.

Which of the following is the most appropriate management?

(A) Combination chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
(B) Left pneumonectomy
(C) *Helicobacter pylori* eradication treatment
(D) Rituximab

Item 33

A 37-year-old woman is evaluated in the emergency department for fever 1 week after her second cycle of chemotherapy for breast cancer. She has no focal symptoms, is otherwise healthy, and takes no medications. The patient lives with her partner 20 minutes from the hospital.

On physical examination, temperature is 38.3 °C (101 °F); other vital signs are normal. She appears well. There is a healed right mastectomy incision, and the left chest port is in place without erythema or tenderness.

Laboratory studies show a leukocyte count of 1,600/µL (1.6×10^9/L) with an absolute neutrophil count of 600/µL (0.6×10^9/L), hemoglobin level of 11.1 g/dL (111 g/L), and platelet count 167,000/µL (167×10^9/L). Urinalysis and basic metabolic panel are normal. Blood cultures are obtained.

Chest radiograph is normal.

Which of the following is the most appropriate treatment for this patient?

(A) Begin cefepime; admit the patient
(B) Begin cefepime and gentamicin; admit the patient
(C) Begin ciprofloxacin and amoxicillin/clavulanic acid; discharge the patient home
(D) Discharge the patient home with close follow-up

Item 34

A 64-year-old woman is evaluated in the office following a diagnosis of metastatic breast cancer. Six years ago, she was diagnosed with breast cancer and treated with lumpectomy, irradiation, and a complete course of adjuvant hormonal therapy. Two weeks ago, a bone lytic lesion was found on a lumbar spine radiograph taken for low back pain after a fall while playing tennis. Subsequent CT scans revealed diffuse involvement of her axial skeleton with no associated fractures and no epidural extension. The patient is currently asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are within normal limits, and examination findings are unremarkable.

Systemic therapy for metastatic breast cancer is planned.

Which of the following is the most appropriate additional treatment?

(A) Calcium and vitamin D
(B) Spine irradiation
(C) Teriparatide
(D) Zoledronic acid

Item 35

A 46-year-old woman is evaluated for swelling and discomfort around her left breast prosthesis. She underwent bilateral prophylactic mastectomies with subsequent textured implant reconstruction 8 years ago by choice related to family history of ductal carcinoma in situ. Medical history is otherwise unremarkable.

On physical examination, vital signs are normal. There is moderate swelling and tenderness around the left breast prosthesis. There are no nodules, erythema, or other skin changes.

Complete blood count is normal.

Ultrasound of the left chest wall shows a moderate-sized fluid collection around the prosthesis. There is no evidence of prosthetic rupture. Aspiration of the fluid shows serous, nonpurulent fluid.

Which of the following is the most likely diagnosis?

(A) Anaplastic T-cell lymphoma
(B) Autoimmune serositis
(C) Breast cancer
(D) Infection of the breast implant

Item 36

A 27-year-old woman is evaluated following a recently confirmed diagnosis of early-stage nodular sclerosing Hodgkin lymphoma. She has had no fevers, night sweats, or weight loss. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is a healing surgical scar over the mid left neck. A 3- × 2-cm left supraclavicular lymph node is palpable. There is no other adenopathy and no hepatosplenomegaly.

Complete blood count is normal. Erythrocyte sedimentation rate is 22 mm/h.

CT and PET scans detect left cervical and supraclavicular adenopathy as well as an anterior mediastinal mass measuring 5 × 4 cm. No infradiaphragmatic disease is noted.

Which of the following is the most appropriate management?

(A) Checkpoint inhibitor immunotherapy
(B) Combination chemotherapy followed by autologous hematopoietic stem cell transplantation
(C) Combination chemotherapy followed by radiation therapy
(D) Radiation therapy alone

Item 37

A 38-year-old man is evaluated for abdominal pain of several weeks' duration.

On physical examination, vital signs are normal. The abdomen is diffusely distended and firm with a 10-cm palpable lower abdominal mass.

Laboratory studies reveal a creatinine concentration of 1.8 mg/dL (159.1 µmol/L), a potassium concentration of 4.9 mEq/L (4.9 mmol/L), and a uric acid concentration of 8.2 mg/dL (0.48 mmol/L).

Results of the chest radiograph are normal. CT scan of the abdomen shows diffuse, bulky mesenteric and retroperitoneal adenopathy. Biopsy of the mass reveals Burkitt lymphoma.

Multiagent chemotherapy containing doxorubicin is planned.

Which of the following is the most likely immediate treatment-associated complication?

(A) Cardiotoxicity
(B) Hypercalcemia
(C) Tumor lysis syndrome
(D) Superior vena cava syndrome

Item 38

A 70-year-old man undergoes routine follow-up evaluation of low-risk prostate cancer diagnosed 3 years ago. He reports no symptoms. He has been managed with active surveillance. His last biopsy was 18 months ago. His prostate-specific antigen (PSA) level was 4.5 ng/mL (4.5 µg/L) 1 year ago and is now 9.2 ng/mL (9.2 µg/L). He takes no medications.

On physical examination, vital signs and all examination findings are unremarkable.

Which of the following is the most appropriate management?

(A) Bone scan
(B) Free PSA measurement
(C) Repeat prostate biopsy
(D) Repeat PSA measurement in 6 months

Item 39

A 71-year-old man is evaluated during a follow-up visit. He underwent radical prostatectomy for prostate cancer 10 years ago. Androgen deprivation therapy was initiated 6 years ago for rising prostate-specific antigen (PSA) levels. His PSA fell rapidly and became undetectable until 6 months ago, when it rose from 0.7 ng/mL (0.7 µg/L) to its present level of 5 ng/mL (5 µg/L). Testosterone remains suppressed. Medical history is otherwise unremarkable, and his only medication is leuprolide acetate.

On physical examination, vital signs are normal, and all examination findings are unremarkable.

CT and bone scan show no evidence of metastatic disease.

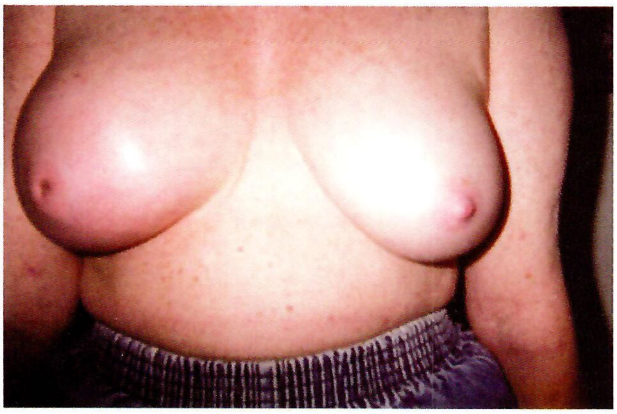
Which of the following is the most appropriate treatment at this time?

(A) Androgen receptor blocker
(B) Bone-seeking isotope
(C) Chemotherapy
(D) CYP17 inhibitor

Item 40

A 50-year-old woman is evaluated for heaviness and swelling of her left breast of 3 weeks' duration. One week ago, she noticed that her outer breast had a pink appearance. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Breast findings are shown.



Breast examination reveals no masses or tenderness.

Results of the complete blood count with differential are normal.

Which of the following is the most likely diagnosis?

(A) Breast abscess
(B) Ductal ectasia

(C) Inflammatory breast cancer
(D) Mastitis

Item 41

A 69-year-old woman undergoes follow-up evaluation for stage III colon cancer, which was resected 2 years ago. She is asymptomatic and takes no medications.

On physical examination, vital signs and examination findings are unremarkable.

Surveillance CT scan of the chest, abdomen, and pelvis reveals a new 3-cm lesion and a 2.5-cm lesion, both in the right lobe of the liver. No other abnormalities are noted.

Which of the following is the most appropriate treatment?

(A) Hepatic artery embolization
(B) Needle biopsy of the largest lesion
(C) Resection of the two lesions
(D) Systemic chemotherapy

Item 42

A 67-year-old woman is about to begin highly emetogenic chemotherapy with cyclophosphamide and doxorubicin for stage III breast cancer.

On physical examination, vital signs are normal. There is a healed left lumpectomy incision and a sentinel node sampling incision. The left chest port is in place.

Which of the following is the most appropriate management of this patient's potential for nausea and vomiting?

(A) Lorazepam
(B) Medical marijuana
(C) Ondansetron, aprepitant, olanzapine, and dexamethasone
(D) Ondansetron or dexamethasone

Item 43

A 66-year-old man is evaluated for increased confusion and lethargy over the past 2 days, as well as nausea and vomiting. He has also had diffuse bone pain that began 6 weeks ago and has worsened over the past month. His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 36.4 °C (97.6 °F), blood pressure is 110/60 mm Hg, pulse rate is 110/min, and respiration rate is 16/min. He is somnolent but can be aroused. Mucous membranes are dry, and he has decreased skin turgor. Cardiopulmonary examination is normal.

Results of laboratory studies show an albumin level of 3.8 g/dL (38 g/L), calcium level of 14.8 mg/dL (3.7 mmol/L), and creatinine level of 2.5 mg/dL (221 µmol/L).

Which of the following is the most appropriate initial management?

(A) Denosumab
(B) Intravenous isotonic saline and calcitonin
(C) Intravenous isotonic saline and furosemide
(D) Zoledronic acid

Item 44

A 33-year-old man is evaluated for a 12-week history of night sweats, fevers, and a 2.5-kg (5.6-lb) weight loss without other localizing symptoms. Medical history is otherwise unremarkable, and he takes no medications.

On thorough physical examination, temperature is 38.1 °C (100.6 °F); the remainder of vital signs are normal. Bilateral supraclavicular lymphadenopathy is noted. The examination is otherwise unremarkable.

Complete blood count, comprehensive metabolic profile, and serum α-fetoprotein and β-human chorionic gonadotropin levels are normal.

Testicular ultrasonography is normal. Contrast-enhanced CT scan of the chest, abdomen, and pelvis shows bulky retroperitoneal, mediastinal, and supraclavicular adenopathy.

An excisional biopsy of a supraclavicular node shows poorly differentiated carcinoma.

Which of the following is the most appropriate management?

(A) Chemotherapy with a cisplatin-based germ cell regimen
(B) Chemotherapy with a fluorouracil-based gastrointestinal cancer regimen
(C) Stereotactic radiation therapy to involved lymph nodes
(D) Surgical debulking of nodal disease

Item 45

A 58-year-old woman undergoes follow-up evaluation for recently diagnosed breast cancer following lumpectomy and sentinel lymph node biopsy. Pathology of the primary tumor revealed a 2.3-cm, grade II, estrogen receptor-positive, human epidermal growth factor 2-negative breast cancer. Two sentinel axillary lymph nodes were negative for cancer. Her medical history is otherwise unremarkable, and she takes no medications.

Local irradiation is planned.

Which of the following is the most appropriate management of the patient's systemic therapy?

(A) Chemotherapy alone
(B) Chemotherapy followed by endocrine therapy for 5 years
(C) Endocrine therapy alone
(D) Multigene recurrence assay

Item 46

A 42-year-old man is evaluated for a 3-month history of worsening fatigue, weight loss, back pain, cough, and hemoptysis. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Pulmonary examination reveals decreased breath sounds in the left lung base.

Chest radiograph reveals a moderate-sized left pleural effusion. CT scan of the chest shows left-sided pleural effusion and a large medial lung mass. Multiple osseous metastatic lesions and bilateral adrenal metastases are also identified. Brain MRI is negative for metastatic disease.

Thoracentesis is positive for adenocarcinoma. Molecular testing is positive only for *ALK* translocation.

Which of the following is the most appropriate treatment?

(A) Alectinib
(B) Combined chemotherapy and pembrolizumab
(C) Platinum-based chemotherapy
(D) Stereotactic radiation therapy

Item 47

A 73-year-old woman seeks advice before beginning a new chemotherapy regimen for metastatic adenocarcinoma of the colon. The new chemotherapy protocol has a modest progression-free survival benefit over a placebo but with increased toxicity. She is currently feeling well, has minor tumor pain controlled with occasional use of ibuprofen, and continues to work full time.

Which of the following results can the patient reasonably expect with the new chemotherapy regimen?

(A) Greater probability of cure
(B) Improved quality of life
(C) Longer life
(D) Longer time without further cancer growth

Item 48

A 73-year-old woman is evaluated in the office following a diagnosis of right-sided breast cancer 2 months ago. The cancer was estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–negative. She is asymptomatic and her only medications are anastrozole, vitamin D, and calcium.

On physical examination, prior right lumpectomy and sentinel node sampling incisions are well-healed. The remaining physical examination findings are unremarkable.

Which of the following is the most appropriate management of this patient's bone health?

(A) Dual-energy x-ray absorptiometry screening
(B) Begin alendronate
(C) Begin denosumab
(D) Substitute raloxifene for anastrozole

Item 49

A 78-year-old man undergoes preoperative evaluation for left knee arthroplasty. Other than knee pain, he has no other symptoms. Medical history is otherwise unremarkable. His only medication is ibuprofen, which he has recently discontinued.

On physical examination, vital signs are normal. Diffuse adenopathy with nodes 1.5 to 2 cm is present in cervical, axillary, and inguinal areas. The spleen is enlarged 2 cm below the left costal margin.

Results of laboratory studies show a leukocyte count of 62,000/µL (62×10^9/L) with 90% lymphocytes, hemoglobin level of 12.8 g/dL (128 g/L), and platelet count 152,000/µL (152×10^9/L). Flow cytometry shows a predominance of CD5, CD19, and CD20 cells expressing only κ light chains consistent with chronic lymphocytic leukemia.

Which of the following is the most appropriate management?

(A) Bone marrow biopsy
(B) Begin ibrutinib
(C) Begin rituximab and bendamustine
(D) Proceed with elective surgery

Item 50

A 34-year-old woman undergoes consultation after a recent diagnosis of stage IB cervical cancer. She is nulliparous, and she and her partner are hoping to have children. Medical history is unremarkable, and she takes no medications.

Colposcopy-directed biopsy of the cervix revealed squamous cell carcinoma with invasion to 6 mm in depth. There is no radiographic evidence of pelvic or abdominal adenopathy and no evidence of distant metastatic disease.

Which of the following is the most appropriate treatment?

(A) Concurrent radiation therapy and cisplatin
(B) Continuous progestin therapy
(C) Fertility-preserving surgery
(D) Hysterectomy and pelvic node dissection

Item 51

A 56-year-old man is evaluated for increasing pain in the mid chest when swallowing. He has not experienced weight loss. Medical history is significant for longstanding gastroesophageal reflux disease. His only medication is over-the-counter famotidine.

On physical examination, vital signs are normal. A 3-cm, left supraclavicular lymph node is palpable. The liver edge is palpable 5 cm below the right costal margin.

Contrast-enhanced CT scan demonstrates a thickening at the gastroesophageal junction and numerous hepatic metastases. The enlarged left supraclavicular node is also noted. An upper endoscopy reveals a mass just above the gastroesophageal junction, and biopsy shows adenocarcinoma.

Which of the following is the most appropriate test to perform next?

(A) Assess tumor for *BRAF* expression
(B) Assess tumor for epidermal growth factor receptor expression
(C) Assess tumor for human epidermal growth factor 2 amplification
(D) PET/CT

Item 52

A 77-year-old woman undergoes follow-up evaluation for recently diagnosed stage I adenocarcinoma of the lung. Medical history is notable for very severe COPD that limits her ability to dress unaided. Her medications are an inhaled corticosteroid, salmeterol, tiotropium, roflumilast, and an albuterol inhaler as needed.

On physical examination, respiration rate is 25/min; other vital signs are normal. Oxygen saturation is 91% breathing 3 L/min of oxygen by nasal cannula. BMI is 20, and she is thin with significant muscle wasting. She has a prolonged expiratory phase of respiration and decreased breath sounds bilaterally.

Surgical and pulmonary consults concur that the patient is too chronically disabled to safely undergo elective thoracic surgery.

Which of the following is the most appropriate treatment?

(A) Combination platinum-based chemotherapy
(B) Combined chemotherapy and radiation therapy
(C) Immunotherapy
(D) Stereotactic radiation therapy

Item 53

A 34-year-old man is evaluated for increasing fatigue, constipation, and weight gain of several months' duration. He has no chest pain, palpitations, dyspnea, or edema. Medical history is significant for classic Hodgkin lymphoma treated with combination chemotherapy and involved site irradiation to the neck 7 years ago. He has been in complete remission since then.

On physical examination, blood pressure is 135/80 mm Hg and pulse rate is 56/min. Other vital signs are normal. There is a healed incision on his left mid neck. The remainder of the examination is normal.

Which of the following is the most appropriate test to perform next?

(A) CT of neck, chest, abdomen, and pelvis
(B) Echocardiogram
(C) PET/CT
(D) Thyroid-stimulating hormone measurement
(E) Thyroid ultrasound

Item 54

A 61-year-old woman is evaluated following a diagnosis of colon cancer. A colonoscopy performed for iron deficiency anemia revealed an adenocarcinoma at the splenic flexure. The patient is asymptomatic and otherwise has no medical problems. Oral iron replacement therapy has been initiated.

On physical examination, vital signs are normal, and the remainder of the examination is noncontributory.

Results of laboratory studies show a hemoglobin level of 9.9 g/dL (99 g/L). A comprehensive metabolic profile and carcinoembryonic antigen measurement are within normal limits.

Which of the following imaging studies should be performed next?

(A) Contrast-enhanced CT of the chest, abdomen, and pelvis
(B) CT colonography
(C) Whole-body PET/CT
(D) No additional imaging studies

Item 55

A 66-year-old woman is evaluated following completion of therapy for locally advanced squamous cell carcinoma of the hypopharynx. She was treated with combined cisplatin chemotherapy and irradiation. One month ago, imaging with PET/CT revealed a complete response. She is a former smoker with a 40-pack-year history who quit 7 years ago. She takes no medications.

On physical examination, vital signs are normal. She has dry oral mucosa and post-irradiation induration to the right of the neck. No cervical adenopathy is noted.

Which of the following imaging tests is most appropriate?

(A) Low-dose CT of the chest in 1 year
(B) MRI of the neck in 3 months
(C) PET/CT in 3 months
(D) No additional imaging is required

Item 56

A 53-year-old man is evaluated after recent surgery for colon cancer. Family history is significant for a paternal uncle with colon cancer at age 47 years and a paternal aunt with a history of uterine cancer.

Postsurgical pathology results show poorly differentiated T3N1 (stage IIIB) colon cancer.

Which of the following is the most appropriate test to perform next?

(A) *BRAF* mutational analysis
(B) Epidermal growth factor receptor mutational analysis
(C) *KRAS* mutational analysis
(D) Mismatch repair protein expression

Item 57

A 53-year-old man is evaluated in the office following hemicolectomy for adenocarcinoma of the colon. He is otherwise healthy, has no symptoms, and takes no medications.

Physical examination is normal.

Presurgical contrast-enhanced CT scan of the chest, abdomen, and pelvis was negative for metastases.

Pathology revealed a 4-cm adenocarcinoma that was poorly differentiated and invading into the submucosa but not into the muscularis. All 17 lymph nodes sampled were negative for tumor. The tumor is staged as T2N0 (stage I). The tumor is negative for *KRAS*, *NRAS*, and *BRAF* mutations.

Which of the following is the most important prognostic factor?

(A) Degree of tumor differentiation
(B) *KRAS*, *NRAS*, and *BRAF* tumor mutational status
(C) Performance status of patient
(D) Size of the tumor
(E) Stage of the tumor

Item 58

A 51-year-old man is evaluated for intermittent, bright red blood per rectum of 10 weeks' duration. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Digital rectal examination is normal.

Stool is positive for fecal occult blood.

A colonoscopy is performed, and a nonobstructing lesion is noted at 10 cm from the anal verge. Examination of the rest of the colon is unremarkable. An MRI scan of the rectum shows the lesion to be invading into but not through the full thickness of the muscularis. No abnormal lymph nodes are seen on MRI. Contrast-enhanced CT scan of the chest and abdomen does not show evidence of metastases.

Biopsy of the mass shows adenocarcinoma.

Which of the following is the most appropriate treatment?

(A) Chemotherapy
(B) Irradiation plus chemotherapy
(C) Irradiation, chemotherapy, and surgery
(D) Surgery

Item 59

A 68-year-old man is evaluated for shortness of breath, headache, and swelling of the neck. He first noticed symptoms 3 weeks ago, which have worsened over the past 2 days.

Medical history is significant for a 25-pack-year history of smoking.

On physical examination, temperature is 36.5 °C (97.8 °F), blood pressure is 110/65 mm Hg, pulse rate is 112/min, and respiration rate is 18/min. Oxygen saturation is 92% breathing ambient air. The patient is cachectic but appears comfortable. His face is plethoric, and there are distended cutaneous vessels over the anterior thorax. An enlarged right supraclavicular lymph node is palpable. Pulmonary examination is normal.

CT scan of the chest reveals bulky mediastinal adenopathy compressing the superior vena cava, right supraclavicular adenopathy, and a small right-sided pleural effusion.

Which of the following is the most appropriate management?

(A) Biopsy of the supraclavicular node
(B) Glucocorticoids
(C) Radiation therapy
(D) Surgical resection of the mediastinal lymphadenopathy

Item 60

A 62-year-old woman is evaluated in the office following a diagnosis of atypical ductal hyperplasia. She underwent a right total hip replacement 2 years ago complicated by deep venous thrombosis. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is a well-healed left breast incision with no skin changes and no palpable mass or nodule.

Which of the following is the most appropriate breast cancer chemoprevention for this patient?

(A) Aspirin
(B) Exemestane
(C) Raloxifene
(D) Tamoxifen

Item 61

A 48-year-old woman is evaluated following the diagnosis of a metastatic neuroendocrine tumor. Two weeks ago, she underwent ultrasonography for biliary colic, which unexpectedly showed multiple hepatic lesions. Gallstones were not present. A subsequent contrast-enhanced CT scan of the abdomen demonstrated multiple hypodense lesions in the liver consistent with metastatic disease. A needle biopsy of a liver lesion showed a well-differentiated, low-grade neuroendocrine tumor with only very rare mitotic figures. Medical history is otherwise unremarkable. The patient feels well without any symptoms, and she takes no medications.

On physical examination, vital signs are normal. Abdominal examination reveals a palpable, firm liver edge 5 cm below the right costal margin.

Results of laboratory studies show a minor elevation of transaminases and alkaline phosphatase.

Which of the following is the most appropriate management?

(A) Hepatic artery embolization
(B) Hormonal therapy with a somatostatin analogue
(C) Peptide-receptor radiotherapy
(D) Repeat imaging in 3 months
(E) Systemic chemotherapy

Item 62

A 72-year-old woman is evaluated for rectal bleeding with bowel movements.

On physical examination, vital signs are normal, and the remainder of the examination, including digital rectal examination, is unremarkable.

A colonoscopy is performed, and a bulky lesion is noted 10 cm from the anal verge. The rest of the colonoscopy results are normal.

MRI of the pelvis shows a bulky tumor in the upper third of the rectum, involving the full thickness of the rectal wall, and several enlarged mesorectal lymph nodes of up to

2 cm in diameter are noted. CT scan of the chest and abdomen is normal.

A biopsy of the mass shows adenocarcinoma.

Which of the following is the most appropriate treatment?

(A) Chemotherapy followed by irradiation and then surgery
(B) Surgery alone
(C) Surgery followed by irradiation
(D) Surgery followed by irradiation and then chemotherapy

Item 63

A 61-year-old man is evaluated in the emergency department for chronic low back pain, which has worsened rapidly over the past week and is now associated with new-onset weakness in his legs. Medical history includes metastatic non–small cell carcinoma of the lung. Previous to this event, the patient had good functional status.

On physical examination, vital signs are normal. He has 4/5 muscle strength with flexion at the bilateral hips and knees.

MRI of the entire spine reveals a 5-cm mass centered in the posterior elements of L1 and L2 with extension into the epidural space and spinal cord compression.

Which of the following is the most appropriate treatment for this patient?

(A) Dexamethasone
(B) Dexamethasone, surgical resection, and irradiation
(C) Irradiation
(D) Surgical resection

Item 64

A 60-year-old woman is evaluated for right-sided mid back pain of 2 months' duration. Medical history is significant for hypertension treated with hydrochlorothiazide. She takes no other medications.

On physical examination, vital signs are within normal limits. Oxygen saturation is 99% with the patient breathing ambient air. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	20 g/dL (200 g/L)
Leukocyte count	7200/µL (7.2×10^9/L)
Platelet count	295,000/µL (295×10^9/L)
Urinalysis	3+ blood; no protein; 30 erythrocytes/hpf; no casts or dysmorphic erythrocytes

Subsequent measurement of erythropoietin level was 180 mU/mL (180 U/L).

Which of the following is the most likely diagnosis?

(A) Lung cancer
(B) Myelodysplastic syndrome
(C) Polycythemia vera
(D) Relative erythrocytosis
(E) Renal cell carcinoma

Item 65

A 62-year-old woman is evaluated for left lower pelvic pain for the last 3 months. Family history is significant for ovarian cancer in her mother at age 51 years and triple-negative breast cancer in her sister at age 42 years.

On physical examination, vital signs are normal. Pelvic examination is notable for a left adnexal mass.

Results of laboratory studies show a CA-125 level of 135 U/mL (normal, <20 U/mL). Complete blood count and liver chemistry test results are normal.

CT scan of the chest, abdomen, and pelvis reveals an 8-cm left adnexal mass. There is no evidence of abdominal or pelvic adenopathy or distant metastases.

Which of the following is the most appropriate initial management?

(A) *BRCA1/2* testing
(B) CT-guided biopsy of the mass
(C) Neoadjuvant chemotherapy
(D) Surgical removal of the mass

Item 66

A 48-year-old man is evaluated for an asymptomatic neck mass that developed 3 weeks ago. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There is a 2-cm firm, fixed, and nontender mass on the right side of his neck.

Results of laboratory studies are within normal limits.

CT of the neck reveals a 2-cm partially cystic neck mass on the right side with suggestion of invasion into surrounding tissue.

Which of the following is the most appropriate initial management?

(A) Fine-needle aspiration
(B) Observation for 1 month
(C) PET/CT
(D) Removal of the mass

Item 67

A 70-year-old woman undergoes consultation following a diagnosis of breast cancer. She has no other medical conditions.

Core biopsy of a left breast mass revealed grade III, estrogen receptor–positive, progesterone receptor–positive, and human epidermal growth factor receptor 2–positive invasive ductal carcinoma. Left lumpectomy revealed invasive ductal carcinoma measuring 1.9 cm in size. Two sentinel nodes were negative.

Which of the following is the most appropriate adjuvant treatment or management for this patient?

(A) Chemotherapy and anti-human epidermal growth factor receptor 2–antibody, breast irradiation, and endocrine therapy
(B) Endocrine therapy
(C) Obtain a gene expression profile
(D) Radiation therapy followed by endocrine therapy

Item 68

A 72-year-old man was diagnosed 9 years ago with prostate cancer. After radiation treatment, his prostate-specific antigen (PSA) level dropped to a nadir of 1.5 ng/mL (1.5 µg/L); it had remained stable until it rose to 2 ng/mL (2 µg/L) 1 year ago and is currently 3.2 ng/mL (3.2 µg/L). He has no symptoms. Medical history is unremarkable, and he takes no medications.

Vital signs and all other physical examination findings are normal. Results of all other laboratory studies are within normal limits.

Biopsy of the prostate is negative. CT of the chest, abdomen, and pelvis and bone scan are negative for metastatic disease.

Which of the following is the most appropriate management?

(A) Androgen deprivation therapy
(B) Chemotherapy
(C) Cryotherapy
(D) Monitor PSA level without treatment

Item 69

A 47-year-old man is evaluated during a follow-up examination. His medical history is significant for resection of cutaneous malignant melanoma from his left upper back 4 years ago. One month ago, he was diagnosed with metastatic melanoma to the liver and lungs. He takes no medications.

No mutation in the liver metastasis *BRAF* gene was identified.

Which of the following is the most appropriate treatment for this patient?

(A) Anti-CTLA-4 antibody plus anti–programmed death antibody
(B) *BRAF* inhibitor
(C) Combination of a *BRAF* and *MEK* inhibitor
(D) *MEK* inhibitor

Item 70

A 54-year-old postmenopausal woman had an abnormal screening mammogram that revealed new calcifications in multiple areas of her right breast. A biopsy showed estrogen receptor–positive ductal carcinoma in situ with high nuclear grade. She underwent a bilateral mastectomy and a right sentinel node biopsy, which revealed ductal carcinoma in situ of the right breast and two negative sentinel nodes.

On physical examination, there are healing bilateral mastectomy incisions with tissue expanders in place.

Which of the following is the most appropriate next treatment for this patient?

(A) Anastrozole
(B) Radiation therapy
(C) Tamoxifen
(D) No adjuvant treatment

Item 71

A 55-year-old woman is evaluated in the office following treatment for limited-stage small cell lung cancer. She was treated with cisplatin/etoposide chemotherapy plus irradiation to the site of the primary tumor. Repeat imaging at the end of treatment showed complete response. She is currently asymptomatic.

Which of the following is the most appropriate management?

(A) Maintenance chemotherapy
(B) PET/CT in 6 months
(C) Prophylactic cranial irradiation
(D) Repeat bronchoscopy

Item 72

A 37-year-old woman is seen for follow-up evaluation 6 months after resection of cutaneous melanoma. It had a 0.45-mm depth of invasion by Breslow microstaging (stage IA).

On physical examination, vital signs are normal. There is a healed incision on the right thigh from resection of the melanoma. There is no evidence of cutaneous or in-transit recurrence and no femoral or inguinal adenopathy.

Which of the following is the most appropriate cancer surveillance for this patient?

(A) Annual chest radiograph
(B) Brain MRI every 6 months for 3 years; PET/CT annually for 5 years
(C) Complete blood count, biochemistry profile, and lactate dehydrogenase measurement every 6 months
(D) Physical examination and dermatologic evaluation every 6 months
(E) PET/CT annually for 5 years

Answers and Critiques

Item 1 Answer: B

Educational Objective: Treat cancer in a patient with reversible poor performance status.

The most appropriate management is fluorouracil and oxaliplatin (**Option B**). This patient has advanced metastatic adenocarcinoma of the colon and a debilitated performance status; however, it is clear that the debilitation is due to tumor burden in an otherwise medically fit individual. The patient, previously well and active with no comorbid medical conditions, developed a rapid decline in health associated with the onset of tumor-related symptoms. This is the sort of situation in which aggressive management with combination chemotherapy (fluorouracil and oxaliplatin) is indicated. Only a major response to chemotherapy has the potential to reverse the debilitation, and if the tumor does respond to treatment, the patient's performance status is expected to improve toward her precancer, healthy state. This is a marked contrast to a patient who is severely debilitated by a combination of a cancer with heavy tumor burden associated with precancer comorbidities that reduced performance status before development of the cancer.

Single-agent, low-dose chemotherapy (**Option A**) would be insufficient in terms of a meaningful impact on reducing tumor burden and improving performance status.

Nonmetastatic colon cancers are managed with initial surgery. Pathologic evaluation determines further treatment. In patients with metastatic colon cancer, surgery on the primary tumor (**Option C**) is unnecessary in the absence of obstruction and would delay the start of needed chemotherapy.

In a patient with serious preexisting comorbidities that limited performance status before the development of cancer—especially if there is concurrent kidney or hepatic dysfunction—supportive care and hospice management (**Option D**) would be recommended. However, all indications suggest that this patient's disability is directly related to the effects of the tumor, and improvement in functional status and quality of life is expected with combination chemotherapy.

KEY POINT

- In the treatment of cancer, it is important to differentiate patients with a poor performance status who are debilitated due to chronic precancer comorbidities from patients who would otherwise be medically fit but are acutely debilitated by their cancer.

Bibliography

Kullmann T, Gauthier H, Serrate C, et al. To treat or not to treat metastatic cancer patients with poor performance status: a prospective experience. Pathol Oncol Res. 2017;23:139-44. [PMID: 27605003] doi:10.1007/s12253-016-0111-4

Item 2 Answer: A

Educational Objective: Evaluate a patient with gross hematuria while taking an anticoagulant.

This patient requires prompt referral to a urologist for cystoscopy (**Option A**) in the evaluation of unexplained gross hematuria. Hematuria is defined as the presence of ≥3 erythrocytes/hpf in the urine sediment and may be microscopic (detectable only on urine testing) or macroscopic (grossly visible). A single incidental finding of hematuria is sufficient to warrant further investigation. Evaluation should be pursued even in patients with bleeding diatheses, or in those taking antiplatelet or anticoagulation therapy. If menstruation, viral illness, vigorous exercise, or some other benign cause is suspected, urinalysis should be repeated after the cause is resolved. If infection is confirmed, urinalysis should be repeated after treatment to document resolution of hematuria. Although CT urography (contrast CT with kidney-specific imaging) has the highest sensitivity and specificity for renal malignancy, noncontrast helical CT is more appropriate if a kidney stone is suspected. Ultrasonography is a reasonable first imaging step because of availability, lower cost, and no ionizing radiation. Cystoscopy is indicated when imaging results are negative.

Discontinuing rivaroxaban and choosing warfarin (**Option C**) as an alternative anticoagulant is not appropriate. Gross hematuria requires a thorough evaluation regardless of the use of anticoagulant therapy. Finally, there is no evidence that warfarin is any safer than rivaroxaban in preventing hematuria.

The American College of Physicians and the American Urological Association recommend against obtaining urine cytology (**Option D**) in the initial evaluation of hematuria due to poor sensitivity.

Reassurance without additional intervention (**Option E**) or repeating a urinalysis (**Option B**) is not appropriate, as a single episode of gross hematuria should trigger an evaluation for the cause.

KEY POINTS

- A single incidental finding of hematuria is sufficient to warrant investigation into its cause.
- Evaluation of hematuria should be pursued even in patients with bleeding diatheses or those taking antiplatelet or anticoagulation therapy.

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Item 3 Answer: D

Educational Objective: **Avoid unnecessary imaging in a patient with stage 0 to II invasive breast cancer.**

Patients with newly diagnosed stage 0 to II breast cancer without symptoms suggestive of metastatic disease and normal comprehensive metabolic profile and alkaline phosphatase measurement should not undergo routine imaging (**Option D**). This patient has stage I breast cancer. Consensus guidelines recommend against routine staging scans for asymptomatic patients with early-stage (0-II) breast cancer given the low incidence of asymptomatic metastases and the risk of false-positive findings on routine staging studies.

The prevalence of a positive bone scan for asymptomatic women with apparent stage I, II, and III breast cancer has been reported as 5%, 6%, and 14%, respectively. Chest radiography is rarely abnormal in asymptomatic patients with stage I or II breast cancer and positive in 7% of patients with stage III disease. Bone scans should be restricted to patients with either localized bone pain or elevation of alkaline phosphatase levels, and chest imaging should be restricted to patients with pulmonary symptoms (**Option A**).

CT of the chest, abdomen, and pelvis (**Option B**) is not recommended for this patient given the small proportion of patients with stage I breast cancer and asymptomatic metastatic disease. Advanced imaging would be indicated in patients with abdominal or pelvic symptoms, abnormal physical examination, or unexplained elevation of aminotransferase or alkaline phosphatase levels. Patients with stage III breast cancer have an elevated risk of asymptomatic distant metastases (14% in one study) and are therefore recommended to undergo routine imaging. CT of the chest, abdomen, and pelvis is most commonly used as the approach to staging. The role of PET/CT is not as well defined in staging patients with breast cancer.

MRI of the brain (**Option C**) is not recommended for patients with newly diagnosed breast cancer in the absence of symptoms suggestive of central nervous system involvement (brain metastases or leptomeningeal disease). Brain metastasis occurs in only a small proportion of patients with metastatic breast cancer and generally later in the disease course.

KEY POINTS

- Imaging studies for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.
- Brain metastasis occurs in only a small proportion of patients with metastatic breast cancer and generally later in the disease course.

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Item 4 Answer: C

Educational Objective: **Treat stage III colon cancer.**

This patient has stage IIIB colon cancer, and the most appropriate treatment is oxaliplatin, fluorouracil, and leucovorin (FOLFOX) (**Option C**). Stage III is defined by metastases to the local-regional lymph nodes. Stage III colon cancer is potentially curable, although the risk of treatment failure increases with the number of positive nodes. Currently, all patients with stage III disease are recommended to receive adjuvant chemotherapy after definitive surgery, as large randomized trials have shown that this treatment modestly improves the likelihood of cure. The combination of oxaliplatin plus a fluoropyrimidine such as 5-fluorouracil (5-FU) or its oral prodrug, capecitabine, has long been the accepted standard postoperative management for stage III colon cancer. The most commonly used regimen is the FOLFOX regimen of 5-FU, leucovorin, and oxaliplatin. 5-FU is given with the reduced folate leucovorin, which is inactive alone but causes 5-FU to bind more tightly to its target enzyme. Oxaliplatin with oral capecitabine is also an acceptable regimen for adjuvant treatment of stage III colon cancer.

Not all drugs that are useful for treating metastatic disease are active in the adjuvant setting. Irinotecan, bevacizumab (**Option A**), and cetuximab have all been shown to be ineffective in improving survival in the adjuvant setting, yet all are part of standard treatment of metastatic disease. For example, the anti-vascular endothelial growth factor monoclonal antibody bevacizumab is often given concurrently with first-line cytotoxic chemotherapy regimens in patients with metastatic colon cancer. This agent has essentially no antitumor activity in colorectal cancer on its own, but it does potentiate other chemotherapies, resulting in a modestly increased duration of progression-free survival, and in some studies, in increased duration of overall survival. Because bevacizumab is not an effective adjuvant treatment for stage III colon cancer, treatment with this agent is not appropriate.

Capecitabine (**Option B**) without oxaliplatin would be insufficient treatment for stage III colon cancer in the absence of some specific contraindication to receiving oxaliplatin.

Unlike rectal cancer, local recurrence in colon cancer is rare, so radiation therapy (**Option D**) is not a routine part of colon cancer management.

Randomized clinical trials demonstrate prolonged disease-free survival and prolonged overall survival in patients who receive adjuvant chemotherapy for stage III cancer. No further therapy (**Option E**) would be inappropriate in the absence of compelling co-morbidities, which would increase the risk of treatment toxicity and shorten survival, independent of the colon cancer.

KEY POINTS

- The FOLFOX regimen of 5-fluorouracil, leucovorin, and oxaliplatin or oxaliplatin with oral capecitabine is the most appropriate adjuvant therapy for stage III colon cancer.
- Unlike rectal cancer, adjuvant irradiation is not part of the routine management of colon cancer.

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Item 5 Answer: E

Educational Objective: Evaluate cancer of unknown primary.

The most appropriate management is no additional testing and to initiate combination chemotherapy (**Option E**). This patient has advanced metastatic adenocarcinoma from a cancer of unknown primary (CUP). Diagnostic efforts should focus on identifying whether a patient is among the approximately 20% of patients with CUP who have a more favorable prognosis and who can benefit from a specific treatment strategy. A biopsy obtained from the site that can be sampled in the safest, least invasive manner is performed, and specimens are evaluated by immunohistochemical stains consistent with the tumor's pattern of presentation to attempt to establish a diagnosis of a more treatable subtype of CUP (for example, germ cell tumor or lymphoma). The clinical evaluation should not involve an exhaustive search for a primary site because detection of an asymptomatic and occult primary tumor does not improve outcome. Physicians should discuss with patients and their families that focusing on identification of the primary tumor can distract from the more important issue of managing the metastatic cancer. Efforts to identify primary tumors should focus only on tumors that are suggested by the clinical presentation or could be managed with a specific, effective therapy. In this case, metastatic disease located below the diaphragm is best managed as gastrointestinal cancer without additional testing for a primary cancer.

Nonspecific tumor markers, such as serum carcinoembryonic antigen, CA-19-9, CA-15-3, or CA-125 (**Option A**), are not definitive for identifying a specific site of origin and are not routinely recommended in patients with CUP.

The use of gene expression arrays (**Option B**) has been commercially promoted, but the clinical utility of these tests to identify more effective therapy has not been established, and their routine use in the evaluation of CUP is not recommended. More importantly, identifying the primary source of this patient's metastatic adenocarcinoma will not change the outcome in this case.

In some patients, PET (**Option C**) may suggest the possible primary location, but false-positive results are significant, and PET scan findings are not apt to change the treatment plan in a patient with metastatic adenocarcinoma located primarily below the diaphragm.

In the evaluation of CUP, specific symptoms may be pursued, such as upper endoscopy and colonoscopy (**Option D**) in patients with symptoms or evidence of gastrointestinal bleeding. This patient has no evidence of gastrointestinal bleeding or gastrointestinal symptoms, and extensive evaluation of the gastrointestinal tract is not warranted.

KEY POINT

- In patients with cancer of unknown primary, diagnostic efforts should focus on identifying a limited number of more treatable subtypes of cancer.

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Item 6 Answer: D

Educational Objective: Stage newly diagnosed large B-cell lymphoma with serum lactate dehydrogenase measurement.

Before considering treatment, serum lactate dehydrogenase (LDH) should be measured to help complete the patient's staging and serve as a prognostic marker for those with large B-cell lymphoma (**Option D**). Large B-cell lymphoma represents approximately 30% of non-Hodgkin lymphomas. These patients often present with symptomatic enlarging lymphadenopathy in the neck or abdomen. Approximately 40% may have signs or symptoms of extranodal disease, and one third have systemic symptoms. Sixty percent of patients have advanced (stage III or IV) disease at diagnosis. The B-cell lymphoma 6 gene shows rearrangement or other mutations that lead to overexpression in most patients. Patients with higher LDH levels have a poorer prognosis, and the result is used in calculating the patient's International Prognostic Index score, which incorporates LDH along with age, stage, performance status, and the presence or absence of extranodal involvement. The International Prognostic Index score correlates with progression-free and overall survival after standard therapy. Patients with poor prognosis may be considered for more aggressive treatment.

Bone marrow biopsies (**Option A**) are no longer routinely performed as part of staging for large cell lymphoma, and in most cases, results would not change management. Likewise, in this patient where multiple bony sites of involvement are seen on the PET scan, bone marrow biopsy would not have an impact on his staging.

Brain MRI (**Option B**) is not generally needed as part of the initial staging for non-Hodgkin lymphoma unless the patient has neurologic signs or symptoms. Central nervous system involvement in patients with non-Hodgkin lymphoma occurs more commonly in individuals with high-grade disease, peripheral blood and bone marrow, sinus, or testicular involvement, and coexistent HIV infection. It most commonly manifests with leptomeningeal disease.

There would generally be no need to biopsy another area of involvement, such as the retroperitoneal node (**Option C**), if adequate material were obtained from the axillary node showing large cell lymphoma. Although discordant histology could sometimes be seen at alternate sites (lower grade or follicular elements), this is uncommon and would not be likely to change the initial treatment approach.

KEY POINTS

- The International Prognostic Index score correlates with progression-free and overall survival after standard therapy for large B-cell lymphoma.
- Patients with large B-cell lymphoma and poor prognosis based on the International Prognostic Index score may be considered for more aggressive treatment.

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Item 7 Answer: B

Educational Objective: Treat cancer of unknown origin with features suggesting an ovarian primary.

Chemotherapy with an ovarian cancer regimen (**Option B**) is the most appropriate adjuvant management for this patient. The source of cancer in some patients presenting with metastatic cancer is never identified. This group of patients is classified as having cancer of unknown primary (CUP). On identification of metastatic cancer, a full medical history and physical examination should be obtained. In female patients, breast examination and mammography should be done to search for a breast primary cancer, and a gynecologic evaluation should be performed to look for an ovarian primary. Imaging studies typically include contrast-enhanced CT of the chest, abdomen, and pelvis. For patients with CUP, the identification of a favorable prognostic subgroup allows selection of specific surgical, radiation, or chemotherapy to which patients are more likely to respond. The patient is a woman with CUP who presents with ascites and abdominal carcinomatosis. Although this patient does not have visible abnormalities in her ovaries on CT and no indication of a primary tumor site, she should be presumptively treated for ovarian cancer, which includes debulking the peritoneal tumor followed by chemotherapy, usually with a platinum-based agent and a taxane.

For a patient with substantial evidence of gastrointestinal tract involvement, such as anemia and blood in the stools, endoscopic search for a gastrointestinal primary would be appropriate, and a gastrointestinal cancer regimen (**Option A**) would be appropriate for palliation.

Immune checkpoint inhibitors, such as programmed death receptor 1 inhibitors (**Option C**), are active in certain types of cancers, such as melanoma, kidney, and lung cancers, but are not part of the routine management of CUP site.

Total abdominal irradiation (**Option D**) for adenocarcinoma is not a reasonable option because the radiation tolerance of the small intestines and kidneys is low, and such treatment would therefore cause unacceptable toxicity.

KEY POINTS

- In women with metastatic cancer of unknown primary, breast examination and mammography should be done to search for breast cancer, and a gynecologic evaluation should be performed to look for ovarian cancer.
- Women who have adenocarcinoma with abdominal carcinomatosis and ascites should be presumptively treated for ovarian cancer.

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Item 8 Answer: A

Educational Objective: Treat a patient with high-risk stage III cervical cancer.

This patient has stage III cervical cancer and should be treated with concurrent radiation therapy and platinum chemotherapy (**Option A**). Patients with early cervical cancer are frequently asymptomatic. The most common symptoms are abnormal or heavy vaginal bleeding or vaginal discharge. Pelvic or back pain and bowel or bladder symptoms are presentations of advanced disease. Diagnosis is made by direct biopsy of a visible lesion, colposcopy, or cone biopsy (conization). The 5-year relative survival for all stages of cervical cancer is 67.5%. The anatomic stage is the most important predictor of prognosis. Ninety percent of patients with localized disease survive 5 years. The 5-year survival rate drops to 58% for patients with regional disease and 17% for patients with disease extending outside of the true pelvis or involving the bladder or rectum. Stage III cervical cancer extends to the pelvic sidewall and/or involves the lower third of the vagina and/or causes hydronephrosis or a nonfunctioning kidney. This patient's tumor extends to the pelvic sidewall. The addition of platinum chemotherapy to radiation therapy in this setting reduces the risk of recurrence by 34% and improves overall survival versus treatment with radiation alone (**Option C**). Peripheral sensory neuropathy is a common adverse effect of platinum chemotherapy, and patients should be monitored for the development of peripheral neuropathy. Patients with preexisting diabetic neuropathy may be more likely to experience worsened neuropathy as a result of chemotherapy. In the absence of more severe peripheral sensory neuropathy, platinum chemotherapy should be incorporated into treatment, given the associated improvement in outcomes.

Hysterectomy and pelvic node dissection (**Option B**) are recommended for patients with stage I and II cervical cancer but not for patients with stage III disease. Patients with stage III cervical cancer have extension to the pelvic sidewall, lower third of the vagina, or pelvic adenopathy, are at higher risk for locoregional and distant recurrence, and are treated with concurrent chemoradiation.

Pembrolizumab (**Option D**) is not currently used as adjuvant therapy for patients with stage I to III cervical cancer. Pembrolizumab is approved for use as second-line therapy for patients with advanced cervical cancer with programmed cell death ligand 1–positive tumors.

KEY POINT

- Patients with bulky or locally advanced stage III cervical cancer are treated with cisplatin-based chemotherapy and radiation therapy.

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Item 9 Answer: D

Educational Objective: Treat moderately severe diarrhea related to immunotherapy.

The most appropriate treatment for this patient is to stop ipilimumab and nivolumab and begin intravenous methylprednisolone (**Option D**). He most likely has immunotherapy-induced colitis. Colitis is just one of myriad potential autoimmune complications of immunotherapy. The more common complications include dermatitis/mucositis, autoimmune endocrinopathies (thyroiditis, adrenalitis, and hypophysitis), pneumonitis, and hepatotoxicity. Colitis is a relatively frequent complication with immunotherapy and is most common with the combination of the CTLA-4 antibody ipilimumab and a programmed death-1 antibody such as nivolumab. It can, however, occur with either drug alone. It presents with mild to severe diarrhea and can be life-threatening. Prompt recognition, discontinuation of immunotherapy, and initiation of glucocorticoid therapy are crucial for moderate or severe cases. Infections with enteric pathogens and *Clostridioides difficile* should be ruled out. Stool testing for lactoferrin and calprotectin suggest bowel inflammation and can be used to monitor disease activity. Proctoscopy or colonoscopy with biopsy can confirm the diagnosis.

Oral budesonide (**Option A**) might be considered in patients with mild noninfectious diarrhea (<4 stools daily) associated with immunotherapy but is inadequate for symptomatic patients with moderate to severe diarrhea.

For patients who do not respond to glucocorticoids, addition of a tumor necrosis factor inhibitor such as infliximab (**Option B**) may be helpful. However, high-dose glucocorticoids are the initial therapy of choice.

5-Aminosalicylates such as mesalamine (**Option C**) are believed to have an anti-inflammatory mechanism of action and are the mainstay of treatment of mild to moderate ulcerative colitis. This patient is much more likely to have an immunotherapy-related adverse event (colitis) than ulcerative colitis, and treatment with mesalamine is not indicated and will not be helpful.

KEY POINTS

- The more common immunotherapy-related adverse events include dermatitis/mucositis, autoimmune endocrinopathies (thyroiditis, adrenalitis, hypophysitis), pneumonitis, and hepatotoxicity.
- The most appropriate treatment for immunotherapy-induced adverse events is stopping the checkpoint inhibitors and beginning high-dose glucocorticoid therapy.

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Item 10 Answer: C

Educational Objective: Treat hypogammaglobinemia in a patient with chronic lymphocytic leukemia.

This patient has recurrent pneumonia, chronic lymphocytic leukemia (CLL), and hypogammaglobulinemia, and the most appropriate treatment is intravenous gamma globulin (**Option C**). Many patients with CLL, particularly when the disease is more advanced, develop low antibody levels that can lead to recurrent infections. For patients who have hypogammaglobinemia, randomized trials demonstrate a lower rate of recurrent infections with administration of intravenous gamma globulin every 3 to 4 weeks. Intravenous gamma globulin is usually given with the goal of raising the IgG level to at least 600 mg/dL (6.0 g/L). Seasonal influenza vaccinations as well as COVID-19 and pneumococcal vaccinations (13-valent conjugate vaccine and 23-valent polysaccharide vaccine) should be given to patients with CLL, although it is known that the response to these vaccines may be impaired from the underlying disease and its treatment.

Neutropenia may complicate CLL or its treatment; however, this patient, although having a low percentage of neutrophils on his differential count, does not have absolute neutropenia (<1500 cells/µL). Absolute neutrophil count (ANC) is calculated as the total leukocyte count multiplied by the percentage of polymorphonuclear and band neutrophils. In this case, the ANC is 3200/µL, so granulocyte-colony stimulating factor (**Option A**) would not be indicated.

Ibrutinib (**Option B**) is a first-line treatment as well as later treatment for CLL. However, treatment would have no immediate benefit for this patient's recurrent risk of infection. In fact, the risk of infection, including some cases of *Pneumocystis jirovecii* pneumonia, may be increased during the first 6 months of treatment, although effective remission may be associated with some later reconstitution of humoral immunity.

Splenectomy (**Option D**) would rarely be performed in patients with CLL, except in circumstances such as for immune thrombocytopenia or immune hemolytic anemia unresponsive to other systemic therapies. Splenectomy further increases this patient's risk for infection with encapsulated bacteria and blood-borne parasites.

KEY POINTS

- In patients with chronic lymphocytic leukemia, repeated infections, and hypogammaglobulinemia, regular treatment with intravenous gamma globulin reduces infectious events.
- Seasonal influenza vaccinations as well as 13-valent conjugate vaccine and 23-valent polysaccharide vaccine should be given to patients with chronic lymphocytic leukemia.

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Item 11 Answer: D

Educational Objective: Manage testicular cancer with radical inguinal orchiectomy.

This patient's findings are consistent with testicular cancer, and the most appropriate management is radical inguinal orchiectomy (**Option D**). Patients with testicular cancer most commonly present with swelling or a solid testicular mass. Although pain is commonly present, not all patients report it. Keeping this diagnosis in mind is important even in men who present with testicular pain without a clearly evident mass. Initial evaluation is typically made with scrotal ultrasound. Cancers are characteristically solid, so cystic masses are rarely indicative of cancer. Seminoma and nonseminomatous germ cell tumors have different ultrasound characteristics, but identification of any solid mass contained within the testicle should prompt further evaluation for cancer. Other studies commonly performed are serum tumor markers and other imaging studies, such as CT of the abdomen and pelvis and chest radiograph. In patients who have findings consistent with a possible diagnosis of testicular cancer, resection by radical inguinal orchiectomy is indicated. This step is both diagnostic and therapeutic, as it provides important local tumor control.

Tumors with elevated α-fetoprotein levels are classified as nonseminomatous germ cell tumors. Following resection, patients with early-stage nonseminomatous germ cell tumors can be managed with active surveillance (in selected patients), retroperitoneal lymph node dissection (RPLND), or limited chemotherapy (**Option A**). Adjuvant chemotherapy is recommended in patients with nodal involvement on RPLND. Persistence of tumor marker elevation after orchiectomy without abnormal imaging findings is also an indication for chemotherapy. Staging includes evaluation with chest radiography, CT of the abdomen and pelvis, and tumor marker levels after orchiectomy. Because the staging process has not been completed, chemotherapy is not indicated.

Needle biopsy (**Option B**) is contraindicated due to an increase in risk of recurrence associated with this procedure. Patients who have scrotal violation may be at increased risk of inguinal node metastases from tumor seeding to the scrotum and inguinal nodes.

PET/CT (**Option C**) does not play a role in the initial evaluation of patients suspected of having testicular cancer. It is not a standard test in this setting but does play a role in the evaluation of residual masses after treatment is completed.

KEY POINTS

- Patients with testicular cancer most commonly present with swelling or a solid mass, and the initial diagnostic study is scrotal ultrasonography.
- Testicular cancer is most commonly managed with radical inguinal orchiectomy.

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Item 12 Answer: A

Educational Objective: Evaluate metastatic disease in a patient with a history of breast cancer.

This patient likely has metastatic breast cancer, and a pulmonary nodule should be biopsied to confirm this before initiating treatment (**Option A**). Metastatic breast cancer is treatable but not curable and is treated in a palliative manner to control disease growth and spread and to prolong life, rather than with curative intent. Essentially all patients with metastatic breast cancer should undergo a biopsy of the metastatic site to confirm the presence of metastatic disease and treatment goals. Breast cancer may be heterogeneous and, in some circumstances, important features such as estrogen receptor and human epidermal growth factor receptor 2 status can differ between the initial primary breast cancer and the metastatic lesion. Therefore, biopsying the metastatic site allows treatment to be tailored to the metastatic disease subtype. Biopsy of the pulmonary lesion will not only assess whether there has been such a subtype switch, but it will also confirm stage IV disease. If choosing among biopsy site options, the lesion that upstages the patient to the greatest degree should be biopsied.

The right axillary mass does not need to be biopsied if the diagnosis of metastatic breast cancer is established through biopsy of one of the pulmonary nodules (**Option B**). A positive biopsy result of a regional nodal recurrence does not establish the diagnosis of metastatic disease and would not avoid the need to biopsy a lung nodule in this case.

This patient should undergo a biopsy to confirm the diagnosis of metastatic breast cancer before initiating treatment. If the patient is found to have metastatic estrogen receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, endocrine therapy plus a CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) would be the preferred option. This combined treatment is associated with substantial improvement in progression-free survival relative to endocrine therapy alone.

Endocrine therapy has long been preferred over first-line chemotherapy in the absence of a visceral crisis, a term used to describe patients with a heavy burden of visceral disease and threatened organ function. However, neither endocrine therapy nor chemotherapy (**Options C, D**) should be initiated before biopsy and confirmation of metastatic breast cancer.

KEY POINTS

- Breast cancer can undergo subtype switch between the primary disease and metastatic disease, and biopsying the metastatic site allows treatment to be tailored to the metastatic disease subtype.
- When evaluating a patient with newly diagnosed metastatic breast cancer, the lesion that upstages the patient to the greatest degree should be biopsied.

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Item 13 Answer: B

Educational Objective: **Treat metastatic mismatch repair–deficient colon cancer.**

This patient now has treatment-refractory metastatic colorectal cancer with a mismatch repair–deficient tumor that should be treated with immunotherapy with a programmed death receptor 1 (PD-1) inhibitor (**Option B**). Tumors may be mismatch repair–deficient either due to a germline mutation, a condition known as Lynch syndrome, or a somatic mutation (or epigenetic silencing) that is limited to the tumor. Because mismatch repair–deficient tumors carry a better prognosis than the more common mismatch repair–proficient tumors, mismatch repair–deficient tumors rarely become metastatic and comprise only 3% to 4% of all metastatic colorectal cancer cases. Patients in this rare subset, however, have shown substantial benefit from treatment with immune checkpoint inhibitors, specifically PD-1 inhibitors. Unfortunately for most patients with metastatic colorectal cancer (>95%) whose tumors are mismatch repair–proficient, PD-1 inhibitors and other immune checkpoint inhibitors have thus far been essentially inactive.

Supportive comfort care and hospice management (**Option A**) is an important consideration in patients who are too sick for treatment or who have exhausted all reasonable treatment options. Such a course of action would not be the most appropriate consideration in a fully functional patient with a meaningful treatment option available.

Stereotactic radiation therapy (**Option C**) can be used for ablation of a limited number of lesions but would not be a reasonable consideration in the patient described who has innumerable lesions in the liver and retroperitoneum.

Tyrosine kinase inhibitors (**Option D**), such oral regorafenib, have very limited antitumor activity in patients such as this but may be a reasonable consideration when all other effective therapies have been exhausted.

KEY POINT

- Immune checkpoint inhibitors, specifically programmed death receptor 1 inhibitors, are indicated for otherwise treatment-refractory metastatic mismatch repair–deficient colon cancer.

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Item 14 Answer: B

Educational Objective: **Screen for bone loss in a patient on an aromatase inhibitor.**

Patients on aromatase inhibitors are recommended to have bone density evaluated with dual-energy x-ray absorptiometry (**Option B**) at the start of treatment to establish a baseline and periodically, every 2 years, while on treatment. Aromatase inhibitors are associated with bone loss and an elevated risk of fracture. The risk of fracture with 5 years of aromatase inhibitor therapy is about 8% to 10%. Patients receiving extended aromatase inhibitor therapy have a higher risk of bone loss and fracture. Consensus guidelines recommend obtaining bone density tests routinely to assess fracture risk. Clinical tools such as the Fracture Risk Assessment Tool can be used to estimate fracture risk using bone density measurement. Fracture risk informs management strategies for osteoporosis and osteopenia, including use of supplemental vitamin D and/or a bone-modifying agent such as a bisphosphonate.

Breast cancer survivors without symptoms suggestive of distant recurrence are not recommended to undergo routine surveillance CTs (**Option A**). Multiple randomized trials have compared an intensive surveillance strategy (with CTs and tumor markers) versus routine care and found no difference in long-term outcomes except that intensive surveillance was associated with inferior quality of life.

Echocardiograms (**Option C**) are not routinely recommended for breast cancer survivors taking aromatase inhibitors or after postmastectomy irradiation. Echocardiograms are performed before receipt of cardiotoxic chemotherapy such as anthracyclines or trastuzumab. Patients with higher cumulative doses and evidence of reduced ejection fraction should have a cardiology consultation. For asymptomatic patients treated with human epidermal growth factor receptor 2–targeted therapy, routine testing posttherapy is not recommended. Potential complications of radiation therapy include coronary artery disease, cardiomyopathy, valvular disease, pericardial disease, and arrhythmias. However, there is no consensus on cardiac testing in asymptomatic patients after chest irradiation.

Pelvic ultrasonography (**Option D**) is not performed routinely for patients on aromatase inhibitors, which do not increase the risk of endometrial cancer. Tamoxifen is associated with a small increase in the risk of endometrial cancer. If a postmenopausal woman on tamoxifen experiences vaginal bleeding, pelvic ultrasonography should be performed to evaluate for uterine abnormalities.

KEY POINT

- Aromatase inhibitors are associated with bone loss and an elevated risk of fracture; patients on aromatase inhibitors should have bone density studies every 2 years.

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Item 15 Answer: B

Educational Objective: Treat a patient with germline *BRCA1* mutation and advanced ovarian cancer.

This patient has advanced epithelial ovarian cancer and a germline *BRCA1* mutation and should receive maintenance therapy with a poly (ADP-ribose) polymerase (PARP) inhibitor (**Option B**). She had optimal debulking, defined as residual tumor deposits less than 1 cm in size, which is associated with improved outcomes. The addition of adjuvant platinum-taxane chemotherapy also improves disease-free and overall survival. For *BRCA1* or *BRCA2* mutation carriers with platinum-sensitive disease (a disease-free interval greater than 6 months), the addition of a maintenance PARP inhibitor following the completion of adjuvant chemotherapy is associated with substantial improvements in progression-free survival. PARPs are involved in repair of single-strand breaks. PARP inhibition leads to DNA breaks that activate homologous recombination (HR) repair. Patients with *BRCA* mutations have defective HR repair, which results in an error-prone repair mechanism that cannot repair these breaks, leading to cell death. In this way, PARP inhibitors are cytotoxic for cancer cells, especially those with a germline or somatic *BRCA1/2* mutation. Maintenance PARP inhibition is also recommended for patients without *BRCA1/2* mutations, but benefits in progression-free survival are lesser.

Irradiation (**Option A**) does not play a role in the adjuvant management of patients with advanced ovarian cancer. Ovarian cancer has a tendency to disseminate within the peritoneal cavity along the peritoneal surface and requires a systemic therapy approach following initial surgery.

Repeat treatment with platinum-taxane chemotherapy (**Option C**) is not recommended in this patient who has responded to initial therapy and has no evidence of recurrent disease. Platinum-based chemotherapy is indicated in patients who relapse 6 months or longer after initial therapy and are more likely to respond to a second course of platinum-based chemotherapy than those who relapse before 6 months. This patient has responded to initial therapy, and the addition of maintenance PARP inhibitor therapy further improves progression-free survival and delays the need for a second course of platinum-based chemotherapy.

No additional therapy (**Option D**) is inappropriate for this patient with advanced epithelial ovarian cancer. The addition of a PARP inhibitor results in substantial improvements in progression-free survival and delays the need for a second course of chemotherapy.

KEY POINT

- Women with advanced ovarian cancer and *BRCA* mutations who achieve some response to platinum-based chemotherapy should receive subsequent maintenance therapy with a poly (ADP-ribose) polymerase inhibitor.

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Item 16 Answer: D

Educational Objective: Assess breast cancer–related risk and risk of congenital malformations following breast cancer treatment.

This patient should be counseled that pregnancy after breast cancer treatment is safe, and there is no increased risk of congenital malformations following breast cancer treatment (**Option D**). The best available data regarding the safety of pregnancy after breast cancer come from matched cohort studies and have found that women with estrogen receptor (ER)-positive and ER-negative breast cancer who become pregnant after breast cancer treatment have outcomes no worse than women who do not become pregnant. These data suggest concerns that pregnancy, a high estrogen state, would increase the risk of recurrence of ER-positive breast cancer are unfounded. Consensus guidelines indicate that pregnancy after breast cancer should not be discouraged. Fertility is a very important survivorship issue and should be discussed with all patients of reproductive age before beginning cancer treatment. Fertility preservation options, including embryo and oocyte cryopreservation, should be discussed as options to preserve fertility before gonadotoxic treatment. Breast cancer survivors' fertility can be diminished as a direct result of chemotherapy, particularly alkylating agents such as cyclophosphamide; however, other drugs including taxanes and platinum chemotherapy may also have an impact on fertility. Trastuzumab and endocrine therapies, such as tamoxifen or ovarian suppression, are not believed to directly impair fertility, although the delay in pregnancy to complete endocrine therapy may be associated with reduced fertility due to an age-related decline in ovarian reserve. The standard for patients with ER-positive breast cancer is to complete the recommended full course of endocrine therapy before trying to conceive.

Breast cancer outcomes, including recurrence and mortality (**Options A, B**), are not increased in patients who become pregnant after treatment.

Pregnancy is contraindicated while on tamoxifen, given an increase in risk of birth defects (genitourinary defects) and should be avoided for a period of 3 months after stopping tamoxifen. There seems to be no increased teratogenicity 1 year after stopping the medication. Pregnancy is contraindicated while on trastuzumab, given an increase in risk of oligohydramnios and for 7 months following the last administration. There is no long-term increase in the teratogenicity risk. Children of female and male cancer survivors treated with chemotherapy, radiation therapy, or both have no increased risk of congenital anomalies or genetic disorders (**Option C**).

KEY POINTS

- Breast cancer outcomes, including recurrence and mortality, are not increased in patients who become pregnant after treatment.
- Congenital malformations are not increased in children of patients after treatment with irradiation or chemotherapy.

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Item 17 Answer: B

Educational Objective: Treat metastatic non–small cell lung cancer without a driver mutation with pembrolizumab plus chemotherapy.

This patient should be treated with pembrolizumab plus chemotherapy (**Option B**). Immunotherapy is playing an increasingly important role in the management of patients with metastatic non–small cell lung cancer. Many different immunotherapy agents, mostly directed against the programmed death-1/programmed cell death ligand-1 (PD-1/PD-L1) axis, have been shown to be effective for the treatment of advanced non–small cell lung cancer. Immunotherapy can be used as single-agent therapy based on expression of the PD-L1 biomarker. However, in patients without a driver mutation (epidermal growth factor receptor, *ALK, ROS1*), the combination of pembrolizumab with carboplatin and pemetrexed has been shown to improve survival in those with metastatic non–small cell lung cancer regardless of PD-L1 level. This was shown in a randomized phase III trial that tested this combination in comparison to carboplatin/pemetrexed in the first-line treatment setting. This study found that the combination of chemotherapy and pembrolizumab improved survival regardless of PD-L1 status. Based on this result, the combination of pembrolizumab and platinum-based chemotherapy is the preferred therapy for patients with good performance status who do not have a driver mutation. Contraindications to immunotherapy include connective tissue disease, rheumatologic diseases, or interstitial lung disease.

Combination chemotherapy (**Option A**) without pembrolizumab has been shown to be inferior to chemotherapy plus pembrolizumab in patients who have good performance status with metastatic non–small cell lung cancer. Use of combination chemotherapy alone is only indicated in patients who are not candidates for immunotherapy treatment. This patient has no apparent contraindication to immunotherapy treatment.

Pembrolizumab alone (**Option C**) can be used in patients with PD-L1 expression greater than 50%. Furthermore, it is also approved as initial therapy in patients with PD-L1 expression from 1% to 49%, although it is less active in this setting, and combined pembrolizumab and chemotherapy is preferred for such patients. This patient has negative PD-L1 expression, however, and single-agent pembrolizumab plays no role in the treatment of such patients.

Single-agent chemotherapy (**Option D**) is not a standard treatment option for first-line treatment of patients with non–small cell lung cancer.

KEY POINTS

- In the absence of a driver mutation (epidermal growth factor receptor, *ALK, ROS1*), combination of pembrolizumab with chemotherapy has been shown to improve survival in patients who have good performance with metastatic non–small cell lung cancer regardless of programmed cell death ligand-1 level.
- In the absence of a driver mutation (epidermal growth factor receptor, *ALK, ROS1*), pembrolizumab monotherapy is first-line therapy in patients with programmed cell death ligand-1 expression greater than 50%.

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Item 18 Answer: C

Educational Objective: Diagnose histologic transformation in low-grade non-Hodgkin lymphoma.

The appropriate next step is to biopsy the left inguinal lymph nodes (**Option C**) to look for evidence of transformation. This patient's clinical picture with rapid growth in a single nodal area with disproportionately higher PET standardized uptake values (SUVs) is suggestive of transformation of his low-grade follicular lymphoma to a more aggressive phenotype, typically to diffuse large cell lymphoma. Other features that can suggest transformation include new onset of B symptoms, declining performance status, marked rise in lactate dehydrogenase, hypercalcemia, and the development of new sites of extranodal disease. SUV on PET scan over 17 is strongly suggestive of transformation, but lower SUV levels cannot reliably rule in or rule out transformation, so biopsy is necessary if there is clinical concern based on other features.

Transformation of low-grade follicular lymphoma to diffuse large cell lymphoma may occur in about one third of patients over time. Transformation has important prognostic and therapeutic implications, as such events indicate a worse prognosis and require more aggressive therapy. If his lymphoma has undergone transformation to a higher grade of disease, combination anthracycline-based chemotherapy, autologous hematopoietic stem cell transplantation, and in some cases, CD19-targerted CAR-T cell therapy would be a treatment option.

Transformation to diffuse large B-cell lymphoma or Burkitt lymphoma is also described in other subtypes of indolent lymphoma including marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia (Richter syndrome), and lymphocyte-predominant Hodgkin lymphoma but is best described in follicular lymphoma.

Treatment strategy depends on the results of the lymph node biopsy. Initiating treatment without a histological diagnosis is not appropriate. Furthermore, treatment with rituximab, rituximab and bendamustine, or irradiation (**Options A, B,** and **D**) may be effective in low-grade lymphoma but not if transformation to higher-grade disease has occurred.

KEY POINTS

- Histologic transformation of follicular lymphoma is suggested by new onset of systemic symptoms, declining performance status, lactate dehydrogenase or calcium elevation, new sites of extranodal disease, or characteristic CT/PET findings.
- Suspected histological transformation of low-grade non-Hodgkin lymphoma should be confirmed by lymph node biopsy.

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Item 19 Answer: D

Educational Objective: Manage depression in a breast cancer survivor taking tamoxifen.

This patient is experiencing depression, and it would be appropriate to prescribe venlafaxine (**Option D**). Depressive symptoms are frequently encountered in patients with chronic medical disease either as a result of the illness itself (such as hypothyroidism) or as a response to the disability caused by the illness. Depression commonly accompanies many medical conditions, including cancer, neurologic diseases (Parkinson disease), heart failure, and HIV infection. Medications, including tamoxifen, glucocorticoids, and interferon, may also trigger depressive symptoms. Some selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, and other antidepressants such as bupropion, are strong inhibitors of CYP2D6 and may interact with tamoxifen, reducing tamoxifen activation. The impact of this interaction on long-term breast cancer outcomes is unknown, but use of strong CYP2D6 inhibitors is generally not recommended, and other SSRIs, such as sertraline or escitalopram, or venlafaxine, a serotonin-norepinephrine reuptake inhibitor, are felt to be safe and are preferred. Breast cancer survivors, particularly those diagnosed at young ages, are at increased risk of anxiety and depression, and evaluating and managing mood symptoms is an important aspect of survivorship care.

Tamoxifen (**Option A**) may cause mood symptoms such as depression, but given the associated improvement in breast cancer outcomes and survival, tamoxifen should not be discontinued in this patient. Mood symptoms could be managed with the addition of an antidepressant. If the patient has depression that persists despite incorporation of antidepressants and/or counseling, it would be reasonable to consider alternatives. In a premenopausal woman, this treatment would include use of ovarian suppression with an aromatase inhibitor, although these medications may also contribute to mood symptoms.

Bupropion (**Option B**) is another antidepressant that is used for the treatment of depression and should also be avoided for patients on tamoxifen, given the possible decrease in tamoxifen activation due to CYP2D6 inhibition.

Fluoxetine (**Option C**) is often used for the treatment of depression but is a strong CYP2D6 inhibitor and is therefore not recommended for patients on tamoxifen because it can decrease tamoxifen activation.

KEY POINTS

- Depression and anxiety are common in women with breast cancer.
- Antidepressants with strong CYP2D6 inhibition, such as bupropion or fluoxetine, may decrease tamoxifen activation and should be avoided.

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Item 20 Answer: C

Educational Objective: Manage a patient with newly diagnosed inflammatory breast cancer.

This patient has inflammatory breast cancer (IBC) and should undergo preoperative chemotherapy followed by mastectomy and irradiation (**Option C**). IBC is diagnosed on the basis of the clinical examination and is usually characterized by erythematous and thickened skin, which is due to occlusion of dermal lymphatic vessels. Patients frequently present with breast enlargement or swelling that is often misdiagnosed as mastitis with subsequent delay in management. A palpable breast mass may be present. One-third of patients have distant metastases at diagnosis, and nearly all have lymph node involvement. For this reason, these patients should have routine staging with either CT and bone scan imaging or PET, even in the absence of symptoms of metastatic disease. IBC is associated with a high risk of both locoregional and distant recurrence and requires multimodality treatment. Patients with IBC should receive preoperative chemotherapy rather than mastectomy followed by chemotherapy and irradiation (**Option A**). Preoperative chemotherapy aims to shrink the tumor to maximize the chance that mastectomy will be a complete resection with negative margins. Mastectomy is associated with decreased risk of locoregional recurrence and improved disease-free survival relative to breast-conserving surgery. Postmastectomy radiation therapy is recommended for cancers greater than 5 cm in size, inadequate or positive margins or skin involvement, IBCs, or four or more positive axillary nodes. Postmastectomy radiation therapy decreases both the risk of local recurrence and the risk of distant metastases and increases overall survival.

Breast-conserving surgery (**Option B**) is not recommended for patients with IBC. Mastectomy is associated with improved locoregional control relative to breast-conserving surgery.

Irradiation should not be the initial therapy. The tumor may decrease in size significantly with up-front chemotherapy allowing greater likelihood of surgical resection. Administering radiation therapy before surgery (**Option D**) increases the risk of poor wound healing and other complications.

KEY POINTS

- Patients with inflammatory breast cancer often present with breast enlargement or swelling that is often misdiagnosed as mastitis.
- Inflammatory breast cancer is usually treated initially with neoadjuvant chemotherapy, followed by surgery, and then radiation therapy.

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Item 21 Answer: A

Educational Objective: Treat a patient with brain metastases and elevated intracranial pressure.

This patient has elevated intracranial pressure from a newly diagnosed brain metastasis and should receive initial treatment with dexamethasone (**Option A**). Elevated intracranial pressure can result from primary brain malignancies or from brain metastases, which occur in 10% to 20% of adult cancer patients. The most common types of primary cancer that cause brain metastases are lung cancer, breast cancer, and melanoma. Median survival after diagnosis of brain metastases varies from less than 3 months to more than 25 months. Symptoms of increased intracranial pressure include headache, depressed global consciousness, and vomiting, and may include signs and symptoms of herniation. In this patient, morning nausea and headache are symptoms that should prompt concern for increased intracranial pressure, which is confirmed by the funduscopic examination showing papilledema. The characteristic findings of late papilledema as shown in the image include elevation of the optic disc with blurring of the margins and loss of the optic cup. Blood vessels are buried as they course the disc. Multiple flame hemorrhages and cotton wool spots, resulting from nerve fiber infarction, are present. Glucocorticoids reduce tumor-related vasogenic edema in 75% of patients and often provide rapid symptom improvement. Although this patient will require irradiation, surgery, or both to directly address the new brain metastasis, glucocorticoids should be initiated upon diagnosis of increased intracranial pressure and should not be withheld for a therapeutic plan to be established.

For the patient with an isolated brain metastasis, the decision to perform surgical resection or stereotactic radiation therapy (**Options B, C**) may depend on the size and location of the lesion, symptom burden, performance status, and comorbidities and is best made through multidisciplinary discussion.

Whole brain radiation therapy (**Option D**) is not ideal for this patient who has an isolated brain metastasis, which could be addressed through surgery or stereotactic radiation therapy. Whole brain radiation therapy is associated with a greater burden of symptoms including fatigue and cognitive impairment. Whole brain radiation therapy is generally used for patients presenting with multiple brain metastases.

KEY POINTS

- Symptoms of increased intracranial pressure include headache, depressed global consciousness, and vomiting, and may include signs and symptoms of herniation.
- Glucocorticoids reduce tumor-related vasogenic edema in patients with brain metastases and often provide rapid symptom improvement.

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Item 22 Answer: C

Educational Objective: Treat locally advanced anal cancer.

This patient has locally invasive squamous cell cancer of the anal canal, and curative-intent treatment with the combination of pelvic radiation therapy and concurrent systemic chemotherapy (**Option C**) is indicated. This would be appropriate for patients with stages I, II, or III anal cancer. Anal cancer is a squamous cell carcinoma, whereas the more common cancer of the rectum is an adenocarcinoma derived from the columnar epithelium of the rectum. Anal cancers are a human papillomavirus (HPV)-associated tumor and are of squamous cell histology. Rectal adenocarcinomas are not HPV-related. Risk of anal cancer is increased in men who have sex with men and in patients with HIV infection, history of condylomata, and kidney or liver transplantation. Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of patients present without any anorectal symptoms. Although no formal recommendations address screening for anal dysplasia in at-risk populations, screening modalities to consider include digital rectal examination, anal Pap test, HPV testing, and high-resolution anoscopy. Mitomycin plus a fluoropyrimidine (now most commonly oral capecitabine, although some centers still use intravenous fluorouracil) is the standard chemotherapy regimen used concurrently with radiation therapy in patients with anal cancer.

Unlike most colorectal cancers, anal cancer, if metastatic, has shown sensitivity to immunotherapy with programmed death receptor 1 inhibitors (**Option A**); however, use of these agents as first-line treatment of local-regional disease is just beginning to undergo investigation and is not a proven or recommended strategy at this time.

Randomized studies have shown irradiation plus chemotherapy to be superior to irradiation alone (**Option B**), and 5-fluorouracil plus mitomycin to be superior to 5-fluorouracil alone.

Surgery (**Option D**) is reserved as a salvage treatment for either local recurrence or incomplete response to chemotherapy plus radiation therapy and is potentially curative. However, because definitive surgery must remove the anal sphincter, a placement of a permanent colostomy would be required. Therefore, surgery is reserved for when other reasonable options have been exhausted.

KEY POINTS

- Anal cancers are a human papillomavirus–associated tumor, and risk is increased in men who have sex with men, in patients with HIV infection, history of condylomata, and kidney or liver transplantation.
- Anal cancer is often curable with combined irradiation and chemotherapy; surgery is typically not indicated.

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Item 23 Answer: C

Educational Objective: Screen for osteoporosis in patients treated with androgen deprivation therapy.

The most appropriate screening test to perform next for this patient is a dual-energy x-ray absorptiometry (DEXA) scan (**Option C**) to establish baseline bone density and to assess for fracture risk. Patients diagnosed with high-risk nonmetastatic prostate cancer are usually treated with a combination of androgen deprivation therapy (ADT) and radiation therapy, which has been shown to improve survival. ADT results in many short- and long-term adverse effects. Short-term effects include loss of lean body mass, fatigue, gynecomastia, hair loss, decreased libido, erectile dysfunction, and vasomotor symptoms. Long-term risks include a possible increase in cardiovascular disease and cognitive dysfunction, increased risk of venous thromboembolism, and reduction in bone density. Patients with nonmetastatic cancer with one or more risk factors for osteoporotic fracture should be offered DEXA screening. ADT is a risk factor for osteoporosis. Patients who are prescribed a drug that causes bone loss or whose bone mineral density is near the threshold of treatment should be screened every 2 years. For patients with osteoporosis, bisphosphonates or denosumab may be offered to reduce the risk of fracture.

There is increasing but inconsistent evidence that ADT is associated with cognitive impairment and Alzheimer disease. However, there is no recommendation for routine dementia screening (**Option A**) in patients taking ATD, and the U.S. Preventive Services Task Force has concluded that there is insufficient evidence for or against routine dementia screening in older adults.

Patients treated with ADT may be at risk for cardiovascular disease and are at increased risk for venous thromboembolism. However, there are no recommendations for screening with either exercise electrocardiography (**Option D**) or Doppler ultrasonography (**Option B**) in asymptomatic patients.

KEY POINTS

- Patients with nonmetastatic cancer with one or more risk factors for osteoporotic fracture should be offered dual-energy x-ray absorptiometry screening.
- Patients with nonmetastatic cancer who are prescribed a drug that causes bone loss or whose bone mineral density is near the threshold of treatment should be screened every 2 years.

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Item 24 Answer: A

Educational Objective: Manage an incidentally discovered neuroendocrine tumor.

The most appropriate management for this patient is expectant observation (**Option A**) and a repeat CT in 3 months. He is incidentally found to have an asymptomatic, well-differentiated, low-grade, small bowel gastrointestinal neuroendocrine tumor (previously known as carcinoid) with multiple small metastases to the liver. Such tumors are often present for many years before diagnosis and are often very indolent. Nonfunctional neuroendocrine tumors are often discovered incidentally. The liver is the most common site of metastases. Asymptomatic patients may have minimal growth and no symptoms for many months or years, even with metastatic disease. Therefore, there is no urgency to intervene, and all interventions carry the potential for risk and expense. A 3-month follow-up examination with repeat imaging is appropriate in asymptomatic patients with relatively low-volume, asymptomatic disease. Approximately one-third to half of metastatic gastrointestinal neuroendocrine tumors will produce serotonin, a hormone that causes diarrhea and/or facial flushing; however, most patients have a hormonally nonfunctional tumor and will not require treatment for these symptoms. In patients who have stable disease at the 3-month scan, further monitoring with serial imaging at 3- to 6-month intervals is appropriate.

Hepatic arterial embolization (**Option B**) is a procedure that may be helpful in shrinking liver metastases or reducing hormonal output from functional tumors. It may be appropriate in a patient with progressive or symptomatic disease but is not indicated in this patient.

Peptide-receptor radiotherapy with a radiolabeled somatostatin analogue (**Option C**) is a potentially useful treatment for patients with progressing or symptomatic disease; however, the toxicity and expense of such an intervention would not be appropriate in an asymptomatic patient with a new diagnosis and a moderate disease burden.

Obstruction of the bowel from a well-differentiated neuroendocrine primary is very uncommon, and so prophylactic surgery to remove the mesenteric mass (**Option D**) in an asymptomatic patient with metastases is not indicated.

KEY POINT

- Well-differentiated, low-grade, metastatic gastrointestinal neuroendocrine tumors are often indolent and asymptomatic and do not require immediate treatment.

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Item 25 Answer: D

Educational Objective: Manage a patient with poor performance status and metastatic non–small cell lung cancer with supportive care/hospice.

Supportive care/hospice care (**Option D**) is the most appropriate management. This patient with metastatic non–small cell lung cancer has poor performance status and should be counseled that supportive care/hospice is in her best interest. Patients with metastatic non–small cell lung cancer can derive significant benefit from treatment, and multiple treatment options are available. These include not just chemotherapy but molecular therapies based on identification of relevant driver mutations and also immunotherapy. Performance status is a means of quantifying how medically fit a patient is overall. A good performance status predicts favorable tolerance and response to treatment. Patients with a poor performance status are much more likely to experience serious or life-threatening toxicity and much less likely to benefit from treatment. In patients with poor performance status and metastatic non–small cell lung cancer, identifying a driver mutation has therapeutic implications. These patients may respond to inhibitors of driver mutations with manageable toxicity and overall benefit. In the absence of driver mutations, combination chemotherapy or immunotherapy is more likely to harm than to help patients with poor performance status.

Immunotherapy can be given as a single-agent therapy and also given in combination with chemotherapy. Neither chemotherapy (**Option B**) nor immunotherapy with bevacizumab (**Option A**) is effective in patients with poor performance status. Combination chemotherapy has been shown to actually worsen outcomes in patients with poor performance status and is not recommended for this patient population.

Radiation therapy (**Option C**) is a palliative treatment, largely for control of pain due to metastatic disease. This patient has widely metastatic disease but is not noted to have significant difficulty with pain. As a result, there is no clear indication for radiation therapy in the treatment of this patient.

KEY POINTS

- Patients with poor performance status and advanced non–small cell lung cancer without a driver mutation do not benefit from chemotherapy or immunotherapy and are best served with supportive care.
- Patients with poor performance status and advanced non–small cell lung cancer with a driver mutation may benefit from therapies that inhibit the mutation.

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Item 26 Answer: D

Educational Objective: Prevent tumor lysis syndrome.

This patient should receive rasburicase (**Option D**) to prevent tumor lysis syndrome (TLS). TLS occurs when tumor cells release their contents into the bloodstream, either spontaneously or as a result of treatment, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These electrolyte abnormalities can lead to acute kidney injury, cardiac arrhythmias, seizures, and death. The risk of TLS can be categorized based on the volume of cancer mass present, the cell-lysis potential of the cancer, and patient characteristics of preexisting kidney failure, dehydration, acidosis, hypotension, or nephrotoxin exposure. TLS is seen most often in patients with highly proliferative hematologic malignancies, such as acute leukemia and high-grade lymphomas, such as Burkitt lymphoma, but can develop in other cancers. Patients at intermediate risk for TLS can be managed with monitoring of laboratory values, hydration, and allopurinol, and those at high risk, such as this patient, should receive vigorous intravenous hydration and rasburicase, a urate oxidase enzyme that metabolizes urate to allantoin, before receiving

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chemotherapy. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, and allopurinol should be used instead.

Acetazolamide (**Option A**) or bicarbonate is not recommended in the prevention of TLS because urine alkalization will increase the risk of hyperphosphatemia and the precipitation of calcium phosphate crystals.

Allopurinol (**Option B**) may be used to prevent TLS in patients at intermediate risk. Allopurinol is not the first-line agent for prophylaxis in patients at high risk for TLS because it does not work as quickly or consistently as rasburicase. Allopurinol prevents the formation of serum urate through xanthine oxidase inhibition but does not reduce existing serum urate levels by metabolizing urate to a more soluble metabolic end product as does rasburicase.

Furosemide (**Option C**) might be considered in some patients to increase urine flow, particularly in those who become volume overloaded with aggressive intravenous volume expansion. This patient displays some evidence of hypovolemia with low blood pressure and tachycardia, however, and furosemide is contraindicated.

KEY POINTS

- Tumor lysis syndrome is seen most often in patients with highly proliferative hematologic malignancies, such as acute leukemia and high-grade lymphomas, such as Burkitt lymphoma.
- Patients at high risk for tumor lysis syndrome should receive vigorous intravenous hydration and rasburicase.

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Item 27 Answer: A

Educational Objective: Treat stage II non–small cell lung cancer with adjuvant cisplatin-based chemotherapy.

The most appropriate management is cisplatin-based chemotherapy (**Option A**). Cisplatin-based adjuvant chemotherapy has been shown in multiple trials to improve survival in patients with resected stage II and stage III non–small cell lung cancer. This survival benefit was confirmed in a large meta-analysis (the LACE meta-analysis), which found that use of a cisplatin-based combination regimen was associated with a clear improvement in survival. Cisplatin can be combined with multiple potential partner agents, none clearly more efficacious than any other. Adjuvant chemotherapy is typically given for four cycles; following that, surveillance is started with periodic CT chest imaging combined with history and physical examination. This patient underwent resection for stage II non–small cell lung cancer, and adjuvant chemotherapy is indicated.

Combined chemotherapy and irradiation (**Option B**) is used to treat locally advanced unresectable non–small cell lung cancer. It is not routinely employed following resection and plays no role in the adjuvant treatment of patients who undergo negative margin resection. Such patients require treatment with adjuvant chemotherapy, not combined chemotherapy and irradiation.

For patients with metastatic non-squamous histology, testing for molecular alterations is mandatory. If an epidermal growth factor receptor (*EGFR*) mutation is identified, initial treatment with erlotinib (**Option C**) is recommended for patients with metastatic disease. If an *ALK* or *ROS1* translocation is identified, initial treatment with alectinib is recommended. This patient does not have metastatic disease, so testing for *EGFR* mutation is not recommended. Erlotinib is not currently a standard adjuvant treatment for patients with resected stage II and III non–small cell lung cancer.

Prophylactic cranial irradiation (**Option D**) is used following treatment for selected patients with treated small cell lung cancer but has not been shown to be beneficial for those with non–small cell lung cancer.

KEY POINT

- Cisplatin-based adjuvant chemotherapy has been shown to improve survival after resection in patients with resected stage II or III non–small cell lung cancer.

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Item 28 Answer: D

Educational Objective: Treat melanoma with a solitary metastasis with surgical resection.

The most appropriate treatment for this patient is surgical resection of the lung lesion (**Option D**). Metastasectomy can be the optimal therapy in appropriately selected patients with solitary or oligometastatic metastases in a variety of malignancies (mostly commonly melanoma, renal cell cancer, colorectal cancer, and sarcomas). Metastatic melanoma can be cured in some cases with metastasectomy. Melanoma may be more likely than some other more common cancers to manifest solitary or oligometastatic disease. The lung is the most common site of visceral metastasis for melanoma, although it has the potential to go anywhere and is more likely than other tumors to involve unusual sites such as the heart and small bowel. Although patients with fully resected metastatic melanoma are prone to develop other sites of disease, some do not. In some cases, repeated excisions of solitary metastases can lead to long-term remission. Solitary pulmonary metastases could also be addressed in some cases by radiosurgery or percutaneous radiofrequency. Positive prognostic factors for patients undergoing metastasectomy include longer disease-free intervals, fewer than three pulmonary nodules, the absence of extrathoracic and lymph node metastases, and a response to chemotherapy or immunotherapy.

Following metastasectomy, data would support the use of adjuvant systemic therapy to improve overall outcome. In this patient with *BRAF* V600E–mutated disease, either immunotherapy or targeted therapy with a *BRAF* or a *BRAF*/MEK inhibitor would be appropriate.

Although the use of immunotherapy with ipilimumab and nivolumab (**Option C**) or a *BRAF* or *BRAF*/MEK inhibitor (if tumor is *BRAF*-mutated) (**Options A, B**) would be appropriate systemic therapy for patients with metastatic melanoma, and in some patients might be associated with durable complete responses, the patient likely has a higher probability of cure via surgical resection followed by adjuvant treatment.

KEY POINT

- Surgical resection of solitary or oligometastatic disease followed by systemic therapy can be curative in many patients with melanoma.

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Item 29 Answer: D

Educational Objective: Manage a young woman with breast cancer while preserving fertility.

This patient should be referred to a reproductive endocrinologist for consideration of embryo/oocyte cryopreservation (**Option D**). Fertility is a key survivorship issue for young patients with cancer. Premenopausal women with breast cancer who receive chemotherapy are at risk of chemotherapy-induced menopause and infertility. Alkylating chemotherapy agents (including cyclophosphamide) are known to be gonadotoxic and are included in most adjuvant chemotherapy regimens for breast cancer. The risk of gonadotoxicity depends on age with very young women (age <35 years) having a low risk of permanent menopause from chemotherapy. All premenopausal women receiving chemotherapy should be counseled on the risk of permanent menopause and infertility associated with chemotherapy and the availability of fertility preservation options. Fertility counseling in this situation is associated with improved psychosocial outcomes. Oocyte and embryo cryopreservation involves ovarian stimulation followed by collection of oocytes, which are then cryopreserved as oocytes or as embryos. Embryo and oocyte cryopreservation may be performed before starting chemotherapy and does not appear to be associated with worse breast cancer outcomes. Aromatase inhibitors are often used during ovarian stimulation in this setting to prevent an increase in estradiol levels. Cryopreservation of oocytes/embryos usually takes 2 to 3 weeks leading to minimal or short delays in care. This is the gold-standard approach for fertility preservation, although it does not guarantee the ability to conceive in the future.

Endocrine therapy itself is not thought to be gonadotoxic. However, pregnancy is contraindicated while on endocrine therapy (**Option A**), which can be teratogenic (tamoxifen) or prevent pregnancy (ovarian suppression). Endocrine therapy is recommended for a period of at least 5 years, during which time fertility can decline due to natural aging, and this process accelerates at age 35 years.

This patient is at risk for treatment-related infertility due to her exposure to the gonadotoxic agents cyclophosphamide and docetaxel. Attempting to conceive after endocrine therapy and exposure to these agents will likely result in decreased fertility (**Option B**).

Gonadotropin-releasing hormone agonists such as depot leuprolide (**Option C**) appear to reduce the risk of treatment-related ovarian insufficiency, but the impact on fertility is less well-defined and should not be recommended as a replacement for embryo or oocyte cryopreservation.

KEY POINTS

- Women with breast cancer of childbearing age who wish to preserve fertility may undergo oocyte or embryo banking before chemotherapy.
- Ovarian stimulation followed by oocyte collection does not appear to be associated with worse breast cancer outcomes.

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Item 30 Answer: D

Educational Objective: Screen for *BRCA* mutation in a patient with high-risk prostate cancer.

This patient should be referred to a genetic counselor to discuss genetic testing for *BRCA1* and *BRCA2* mutations (**Option D**). He has been diagnosed with metastatic prostate cancer. His biopsy revealed high-risk disease based on a Gleason score of 9. Genetic testing for *BRCA* gene mutation should be done in all men with high-risk disease, including patients with a Gleason score >7, positive lymph nodes, or metastatic disease. The risk of an underlying mutation in patients with metastatic disease is 11.8%. A family history of breast cancer in a first-degree relative diagnosed before the age of 50 years is also an indication for genetic counseling and *BRCA* testing. Therefore, based on both personal and family history, this patient is clearly a candidate for *BRCA* testing.

Cystoscopy (**Option A**) is used to evaluate patients suspected of having bladder cancer or symptoms, such as hematuria, that might indicate bladder wall involvement by an adjacent neoplasm. Cystoscopy would not be done to evaluate otherwise asymptomatic prostate cancer.

PET/CT (**Option B**) is not indicated for this patient, as he already has evidence of metastatic disease. PET/CT will not change his management and is not a standard test in this setting.

Prostate-specific antigen (PSA) density (**Option C**) is the PSA divided by prostate volume. This is calculated to correct the PSA for differences in prostate volume between different patients. After definitive treatment for localized prostate cancer, PSA density is used to help with decision-making regarding active surveillance and treatment. This is especially true for asymptomatic men with PSA-only recurrence, as it can take several years for clinical metastatic disease to develop in that setting. PSA density measurement has no role in the evaluation of men with clinical metastatic disease.

KEY POINTS

- Patients with high-risk prostate cancers (high Gleason score, lymph node metastases, or distant metastatic disease) should be referred for genetic counseling, as the risk of a *BRCA* mutation is approximately 12%.
- In men with prostate cancer, a family history of breast cancer in a first-degree relative diagnosed before the age of 50 years is also an indication for *BRCA*-related genetic counseling.

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Item 31 Answer: B

Educational Objective: Screen for breast cancer in a patient with previous chest irradiation.

This patient had previous mantle irradiation treatment for Hodgkin lymphoma (HL), and she should have both mammography and breast MRI (**Option B**). The second leading cause of death for survivors of HL are second cancers. Most second cancers are solid tumors, and among those, the most frequent are breast, lung, and colon cancers. The increased risk begins about 5 to 8 years posttreatment but continues to increase for at least 20 years. Secondary malignancies may develop in cancer survivors either from previous carcinogen exposure or late effects of previous cancer treatments. Women receiving chest irradiation for HL have a markedly increased risk of breast cancer, especially if they received treatment when younger than 35 years, with an increased risk beginning within 8 years of treatment. Annual breast cancer screening is recommended to begin 8 to 10 years post-therapy or at age 40 years, whichever comes first. The National Comprehensive Cancer Network (NCCN) guideline recommends breast MRI in addition to mammography for women who received irradiation to the chest between the ages of 10 and 30 years. The NCCN also recommends consideration of referral to a breast specialist.

Screening mammography (**Option A**) is necessary for early detection of breast cancer in patients treated for HL with mantle irradiation, but a prospective trial demonstrated that the use of MRI, in addition to screening mammograms, identified additional breast cancers when compared with mammography alone in these high-risk patients.

Breast MRI alone (**Option C**), like mammography alone, is insufficient in a patient with previous mantle irradiation for HL. Studies have shown that mammography and MRI complement each other and provide superior early detection of such disease.

Ultrasonography (**Option D**) is the preferred method of evaluation of a breast mass in women younger than 30 years, in whom mammography has low sensitivity due to dense breast tissue. This patient, who is over 30 years of age, does not have a breast mass, so ultrasonography would not be appropriate. Ultrasonography is not recommended as the breast cancer screening strategy after chest irradiation.

KEY POINTS

- For women survivors of Hodgkin lymphoma who received chest irradiation, annual breast cancer screening is recommended to begin 8 to 10 years post-therapy or at age 40 years, whichever comes first.
- Breast MRI is recommended as an adjunct to mammography for breast cancer screening in Hodgkin lymphoma survivors who were treated with chest irradiation between ages 10 and 30 years.

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Item 32 Answer: D

Educational Objective: Treat a low-grade mucosa-associated lymphoid tissue lymphoma involving the lung.

This patient has mucosa-associated lymphoma tissue (MALT) lymphoma, and the most appropriate management is single-agent rituximab (**Option D**). MALT lymphomas are low-grade B lymphomas of the marginal zone type (a category that also includes splenic marginal zone and nodal marginal zone lymphomas). They account for 5% to 8% of B-cell lymphomas and arise from B cells in the "marginal zone," the external part of secondary lymphoid follicles. The stomach is the most common site for MALT lymphomas, and it has been linked to infection with *Helicobacter pylori*. Chronic infection and/or antigenic stimulation may play a role in the development of MALT lymphomas in other sites as well (e.g., Hashimoto thyroiditis and thyroid MALT lymphomas or Sjögren syndrome and parotid lymphomas), but antibiotic therapy has only been definitively proven to be effective for *H. pylori*-associated gastric MALT lymphomas (**Option C**). MALT lymphomas typically have a relatively indolent course, and asymptomatic patients may be observed without treatment, although radiation therapy can be considered for those with localized disease. For other MALT lymphomas, such as in this patient who is symptomatic and has disease in multiple lobes of the lung, single-agent rituximab, an anti-CD20 monoclonal antibody, would be an appropriate treatment. This therapy is generally quite active and well tolerated.

Aggressive combination chemoimmunotherapy with a regimen such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (**Option A**) would not be appropriate as initial treatment of a MALT lymphoma in an elderly patient. R-CHOP is more typically used in patients with more aggressive lymphomas, such as diffuse large cell lymphoma. Although MALT lymphomas can undergo transformation to more aggressive histologies, such changes are not common.

Other than for establishing a diagnosis and managing complications, surgery would generally have little role in the treatment of most low-grade lymphomas. A pneumonectomy (**Option B**) would not be appropriate for a patient with a low-grade lymphoma of the lung. That would be an aggressive, morbid, and generally high-risk procedure.

KEY POINTS

- *Helicobacter pylori* eradication therapy has only been definitively proven to be effective for *H. pylori*–associated gastric mucosa-associated lymphoma tissue lymphomas.
- The treatment of mucosa-associated lymphoma tissue (MALT) lymphomas other than gastric MALT lymphoma may include irradiation for localized disease or rituximab when systemic therapy is required.

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Item 33 Answer: C

Educational Objective: Treat low-risk neutropenic fever in an outpatient.

The most appropriate treatment is to begin ciprofloxacin and amoxicillin/clavulanic acid and discharge the patient home (**Option C**). Selected patients with fever and neutropenia can be managed as outpatients. If the patient is compliant, uncomplicated, hemodynamically stable, does not have significant comorbidities, has no known increased risk to be harboring resistant organisms, and has an anticipated short duration of neutropenia, outpatient management is an option. Published criteria for risk stratification for outpatient management include the Multinational Association for Supportive Care in Cancer index, Talcott's rules, or Clinical Index of Stable Febrile Neutropenia. Published criteria for outpatient management include (1) residence ≤1 hour or ≤30 miles (48 km) from the clinic or hospital, (2) patient's primary care physician or oncologist agrees to outpatient management, (3) ability to comply with logistic requirements, including frequent clinic visits, (4) family member or caregiver at home 24 hours/day, (5) access to a telephone and transportation 24 hours/day, and (6) no history of noncompliance with treatment protocols. Patients should have frequent follow-up by phone or in the office to reassess their status.

Cefepime (**Option A**) is an antipseudomonal β-lactam that is often used as empiric parenteral therapy for febrile neutropenia in hospitalized patients. However, studies have demonstrated that there is a similar level of safety and efficacy with oral versus intravenous regimens as initial empiric therapy for the treatment of low-risk febrile neutropenia.

Clinical studies have also demonstrated that there is no better survival or therapeutic success but rather an increased risk of toxicity from adding an aminoglycoside to a broad-spectrum β-lactam, such as cefepime (**Option B**), in the treatment of febrile neutropenia.

Given the patient's neutropenia and documented fever, observation without antibiotics (**Option D**) would not be appropriate, as patients with fever and neutropenia can become quite ill rather quickly without antibiotics.

KEY POINTS

- For selected patients with low-risk neutropenic fever, recommended empiric outpatient treatment includes a fluoroquinolone (i.e., ciprofloxacin or levofloxacin) plus amoxicillin/clavulanate.
- There is no better therapeutic success but rather an increased risk of toxicity from adding an aminoglycoside to a broad-spectrum β-lactam in the treatment of febrile neutropenia.

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Item 34 Answer: D

Educational Objective: Treat bone metastases from breast cancer.

This patient should receive zoledronic acid (**Option D**). A bone-modifying agent is administered routinely to all patients with metastatic breast cancer and bone metastases to prevent the development of skeletal-related events, including bone pain, cord compression, need for palliative radiation therapy, and hypercalcemia. Appropriate agents include zoledronic acid (a bisphosphonate) or denosumab (a receptor activator of nuclear factor κB ligand inhibitor). Zoledronic acid and denosumab are generally administered every 3 months because of similar efficacy to monthly dosing. Zoledronic acid is cleared through the kidneys and is contraindicated among patients with creatinine clearance less than 30 mL/min. Dose adjustment is not recommended for denosumab in patients with renal insufficiency. Both agents may cause symptomatic hypocalcemia. Additionally, both agents are associated with small risks of osteonecrosis of the jaw, and treatment should generally be held for patients who have active dental issues for which extractions or other dental work is needed. Zoledronic acid is substantially less costly than denosumab and, given similar efficacy, should be the preferred option for most patients.

Patients receiving bone-modifying agents may be at risk for the development of hypocalcemia and, in the absence of hypercalcemia, should be treated with vitamin D and calcium to prevent hypocalcemia. However, calcium and vitamin D alone (**Option A**) are an insufficient preventive therapy for this patient with metastatic bone disease.

This patient has asymptomatic bone metastases and should not receive spine irradiation. Metastatic breast cancer is managed primarily with systemic treatments to control growth and spread of the disease and to prevent treatment symptoms that arise from metastases. Palliative irradiation (**Option B**) is often useful for patients with focal areas of pain caused by bone metastases but is not indicated in this asymptomatic woman.

Teriparatide (**Option C**) is a form of parathyroid hormone and acts as an anabolic agent to promote bone formation for the treatment of osteoporosis. It is not used to treat bone metastases from solid tumors. Additionally, its use is contraindicated for patients with a history of irradiation due to concerns regarding an increased risk of osteosarcoma in the treatment field.

KEY POINT

- For patients who have breast cancer with bone metastases, bone-modifying agents such as zoledronic acid or denosumab are recommended to prevent bone-related events such as bone pain, cord compression, need for palliative irradiation, and hypercalcemia.

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Item 35 Answer: A

Educational Objective: Diagnose anaplastic T-cell non-Hodgkin lymphoma in a patient with textured breast implants.

The most likely diagnosis is anaplastic T-cell lymphoma (**Option A**). Although uncommon, there are increasing reports of non-Hodgkin lymphoma, typically anaplastic T-cell lymphoma, arising around breast implants. The major association has been with textured breast implants, which are now no longer being used. Patients with these lymphomas typically present with swelling and discomfort with a median time of 8 to 9 years after prosthesis placement. Initial evaluation after physical examination is by ultrasound (which appears to be superior to mammography, CT, or MRI) to look for a fluid collection and aspiration if fluid is present. Cytology may confirm malignant cells compatible with anaplastic T-cell lymphoma. These anaplastic T-cell lymphomas are typically CD30+ and *ALK* negative. If the disease is diagnosed early, it may be cured with surgery alone with removal of the implant and complete resection of the surrounding capsule. If a contralateral implant was placed, it should be removed as well. In cases of more advanced disease with nodal involvement, more distant spread, or recurrence, chemotherapy and/or radiation therapy may be indicated. Treatment is not yet standardized, and recommendations continue to evolve for this entity.

Some reports have suggested an increase in Sjögren syndrome, scleroderma, and rheumatoid arthritis syndromes associated with silicone implants; however, such an association was never definitively confirmed. Autoimmune inflammation of the breast implant with associated serositis (**Option B**) is not seen with these conditions.

Prophylactic mastectomies lead to at least a 90% reduction in the risk of developing breast cancer (**Option C**) in patients at high risk. Although breast cancer can arise in residual breast cells even after prophylactic mastectomy, it would be uncommon and more likely to present as a cutaneous or subcutaneous mass rather than a fluid collection.

Although breast implants can become infected (**Option D**), the absence of fever, leukocytosis, and erythema and the presence of serous, nonpurulent fluid are not suggestive of infection in this patient. These infections usually occur shortly after the prosthesis is placed but can develop years later.

KEY POINT

- Anaplastic large cell lymphoma associated with textured breast implants most commonly presents with a periprosthetic fluid collection and is best detected on ultrasound.

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Item 36 Answer: C

Educational Objective: Treat early-stage Hodgkin lymphoma.

For this patient with early-stage Hodgkin lymphoma, the most appropriate treatment options would be combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine followed by radiation therapy (**Option C**). Unfavorable prognostic factors for early-stage Hodgkin lymphoma include the presence of a large mediastinal mass, an elevated sedimentation rate, involvement of multiple nodal sites, extranodal involvement, age 50 years and older, or massive splenic disease. The combination of chemotherapy and irradiation is associated with a high rate of cure in early-stage disease, even with adverse prognostic features. Using both modalities in combination has allowed for high cure rates while using shorter courses of chemotherapy (two to four cycles) and lower cumulative doses of radiation given to smaller fields, thus minimizing the potential for long-term toxicities. Chemotherapy alone could also be an appropriate option for this patient, avoiding irradiation entirely, if she has a complete metabolic response by interim PET/CT after two to three cycles of treatment (risk-adapted therapy). Avoiding radiation therapy may be associated with a slightly higher risk of relapse but avoids the risk of late radiation therapy–induced toxicities.

Treatment with checkpoint inhibitors such as nivolumab and pembrolizumab (**Option A**) may be considered for patients experiencing a second or later relapse and those who relapse after autologous hematopoietic stem cell transplantation. Combination chemotherapy and irradiation, or in some instances, chemotherapy alone is the preferred first-line therapy and is associated with nearly a 75% cure rate.

Chemotherapy with ifosfamide, carboplatin, and etoposide followed by autologous hematopoietic stem cell transplantation (**Option B**) is an option for patients with relapsed, refractory Hodgkin lymphoma, but this is a salvage approach and is not used as first-line treatment.

Although radiation therapy alone (**Option D**) can be curative for early-stage classical Hodgkin lymphoma, the cure rate is higher with the addition of chemotherapy. Furthermore, older studies using radiation therapy alone, with larger fields and higher doses, were associated with an increased risk of late second malignancies as well as organ (cardiac, pulmonary, thyroid) dysfunction. Thus, essentially all patients with early-stage Hodgkin lymphoma currently receive chemotherapy as part of their treatment.

KEY POINTS

- Early-stage Hodgkin lymphoma is most commonly treated with combination chemotherapy followed by radiation therapy.
- Chemotherapy alone is a treatment option for early-stage Hodgkin lymphoma after a complete metabolic response assessed by interim PET/CT after two to three cycles of treatment (risk-adapted therapy).

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Item 37 Answer: C

Educational Objective: Identify Burkitt lymphoma as high risk for tumor lysis syndrome.

The most likely immediate treatment-associated complication for this patient is tumor lysis syndrome (TLS) (**Option C**). TLS is most likely to occur in patients who have larger tumor burdens and more chemotherapy-sensitive disease. It is usually seen in aggressive non-Hodgkin lymphoma, Burkitt lymphoma, as well as some leukemias and is rarely seen in solid tumors. TLS typically manifests in the first 24 to 48 hours after chemotherapy initiation but may even develop spontaneously before treatment. Patients develop hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia, which can be associated with arrhythmias, tetany, and seizures. Kidney failure may ensue from acute urate nephropathy, worsening the metabolic abnormalities. Prevention is with vigorous hydration and rasburicase.

Acute anthracycline toxicity (**Option A**) can present as heart block, arrhythmias, heart failure, myocarditis, and pericarditis. However, this complication occurs in less than 1% of patients and may be reversible. Chronic progressive anthracycline toxicity usually presents as dilated cardiomyopathy, which is most closely linked with the use of doxorubicin. TLS is a much more likely immediate complication in patients with Burkitt lymphoma, with risk estimates generally greater than 5%.

Hypercalcemia of malignancy (**Option B**) occurs in 20% to 30% of patients with advanced cancer. It is most frequent in patients with myeloma and cancer of the lung, breast, kidney, and head and neck. Lymphomas can cause hypercalcemia by overproduction of 1,25-dihydroxyvitamin D. This patient is more likely to experience hyperphosphatemia and hypocalcemia from TLS in the absence of aggressive preventive treatment.

Superior vena cava (SVC) syndrome (**Option D**) is caused by acute obstruction of blood flow to the right atrium from the upper torso, can result in symptoms of progressive dyspnea and cough, and may be associated with swelling of the face and neck. The most common cause of SVC syndrome is lung cancer. Other malignancies less commonly associated with SVC syndrome include diffuse large B-cell lymphoma, lymphoblastic lymphoma, and germ cell tumors. Mediastinal widening and pleural effusions are common radiographic findings. This patient with a normal chest radiograph and elevated serum creatinine and urate level is much more likely to develop spontaneous or treatment-related TLS.

KEY POINTS

- Tumor lysis syndrome is usually seen in aggressive non-Hodgkin lymphoma, Burkitt lymphoma, as well as some leukemias.
- Metabolic complications of tumor lysis syndrome include hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia.

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Item 38 Answer: C

Educational Objective: Manage progressing prostate cancer in a man on active surveillance.

This patient should have a repeat prostate biopsy (**Option C**). Active surveillance is a management option that consists of planned monitoring and deferred therapy for patients with low-grade prostate cancer. Monitoring during active surveillance consists of a repeat biopsy done approximately 1 year from the original diagnosis and, assuming no high-grade tumor has developed, less often thereafter; annual digital rectal examination should be done yearly, and serial prostate-specific antigen (PSA) measurements should be done every 6 to 12 months. Sustained rise in PSA or new abnormalities on digital rectal examination warrant an additional prostate biopsy, perhaps guided by MRI imaging. The goal of active surveillance is to more promptly identify men with evidence of cancer progression that requires treatment while also avoiding treatment in men who do not have progressive cancer. In men with low-risk prostate cancer, active surveillance is a reasonable strategy because some men will never require treatment, and outcomes are no worse if men with low-grade cancer are treated at the time of progression rather than when first diagnosed. This patient has experienced a doubling of PSA in just 1 year. Although PSA alone cannot definitely identify men who require treatment, a doubling time of less than 3 years is grounds for reassessment with a repeat biopsy.

At this time, the patient does not require a bone scan (**Option A**). A bone scan might be warranted if there is documentation of disease progression, such as the assignment to a different risk group based on the results of the prostate biopsy. Until that time, imaging is not indicated.

Measurement of free PSA (**Option B**) may increase the sensitivity of PSA screening for prostate cancer and can be helpful in cases of borderline elevated PSA measurements due to its greater specificity. Measurement of free PSA does not play a role in the management of men who are being managed with active surveillance, however, and is not indicated in this man who already has an indication for repeat biopsy.

Rechecking PSA in 6 months (**Option D**) is not indicated because this man already meets criteria for repeat biopsy.

KEY POINTS

- In men with low-risk prostate cancer, active surveillance is a reasonable strategy because some men will never require treatment, and outcomes are no worse if men with low-grade cancer are treated at the time of progression rather than when first diagnosed.
- In men undergoing active surveillance for prostate cancer, a doubling time of less than 3 years is grounds for reassessment with a repeat biopsy.

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Item 39 Answer: A

Educational Objective: Treat castrate-resistant M0 prostate cancer with apalutamide.

This patient has castrate-resistant M0 prostate cancer and should be treated with an androgen receptor blocker (apalutamide or enzalutamide) (**Option A**). M0 castrate-resistant prostate cancer occurs when the prostate-specific antigen (PSA) level rises without evidence of clinical metastatic disease in men being treated with androgen deprivation therapy (ADT). This condition does not always require treatment, as in men with a very slowly rising PSA level because it can take years before there is development of clinical metastatic disease. However, in a patient with a rapidly rising PSA level (e.g., doubling time ≤10 months), treatment is indicated, as development of clinical metastatic disease typically occurs much sooner. Treatment with androgen receptor blockers improves overall survival in this patient population. A large, randomized, placebo-controlled trial study concluded that apalutamide improved median metastasis-free survival from 16.2 months to 40.5 months. Apalutamide and enzalutamide are both standard treatments for this patient population.

Bone-seeking isotope treatment with radium-223 (**Option B**) is indicated for treatment of castrate-resistant metastatic prostate cancer with bone-only or bone-predominant metastatic disease. This agent is not indicted for treatment of men without metastatic disease.

Chemotherapy (**Option C**) is indicated for treatment of M1 castrate-resistant prostate cancer. This patient does not have M1 disease as discussed previously. In the form of docetaxel, it can also be used in combination with ADT in the initial treatment of men with castrate-sensitive metastatic prostate cancer.

Treatment with a CYP17 inhibitor (abiraterone) (**Option D**) is an established treatment for M1 castrate-resistant metastatic prostate cancer. It is not indicated for M0 castrate-resistant prostate cancer.

KEY POINTS

- Men with nonmetastatic prostate cancer and a very slowly rising prostate-specific antigen level do not always need treatment because development of clinical metastatic disease may take years.
- Androgen receptor blockers have been shown to improve metastasis-free survival in patients with nonmetastatic, castrate-resistant prostate cancer with rapidly rising prostate-specific antigen levels.

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Item 40 Answer: C

Educational Objective: Diagnose inflammatory breast cancer.

This patient most likely has inflammatory breast cancer (IBC) (**Option C**). IBC is suspected on the basis of clinical findings including erythema, peau d'orange, and skin thickening. Patients often present with breast enlargement or swelling developed during a few weeks or months, and younger, lactating women may have been treated for presumed mastitis with antibiotics. It is important to consider that IBC may be the underlying cause in lactating women who do not respond to antibiotics for an apparent mastitis. A palpable breast mass may be present. The skin changes are due to the obstruction of dermal lymphatic vessels by cancer cells. The initial diagnostic test is mammography followed by core biopsy of any suspicious lesion. The finding of dermal lymphatic invasion with a punch skin biopsy supports but is not necessary for the diagnosis of IBC. Patients with IBC have a higher risk of distant recurrence and also a higher risk of locoregional recurrence and should be treated with aggressive local and systemic therapy. All patients with IBC should receive preoperative chemotherapy to optimize the likelihood of obtaining negative surgical margins. Patients with IBC often have a greater extent of disease in the breast, and all should undergo mastectomy and postmastectomy irradiation to minimize the risk of locoregional recurrence.

Mammary ductal ectasia (**Option B**) is an inflammatory breast condition most prevalent in middle-aged women. The genesis of the findings is related to collection of debris in mammary ducts resulting in ductal inflammation. It may be associated with nipple discharge. On occasion, the distended mammary duct can be visualized as a blue mass under the nipple. The blocked ducts may become infected resulting in breast abscess or mastitis. The condition often resolves spontaneously. Mammary ductal ectasia usually results in localized inflammatory changes, not the diffuse changes as noted in this patient.

Infections of the breast, specifically mastitis and breast abscess (**Options A, D**), most commonly occur in lactating women and would be unusual in a 50-year-old woman. Infectious mastitis can have a similar clinical and mammographic appearance to IBC. However, infectious mastitis and breast abscesses are typically associated with breast tenderness, fever, and leukocytosis, whereas IBC—despite its name—is not a true inflammatory process and is not associated with these findings.

KEY POINTS

- Inflammatory breast cancer is suspected on the basis of clinical findings including erythema, peau d'orange, and skin thickening.
- Diagnostic modalities for suspected inflammatory breast cancer include mammography, core biopsy, and skin biopsy.

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Item 41 Answer: C

Educational Objective: **Treat oligometastatic liver metastases.**

This patient has oligometastatic disease in the liver and is a candidate for surgery with curative intent (**Option C**). Postoperative surveillance following curative resection for colorectal cancer is used to identify oligometastatic disease in the liver or lung that may be resectable. Contrast-enhanced CT of the chest, abdomen, and pelvis is recommended annually for up to 5 years postoperatively. Patients with metastatic lesions confined to the liver or lung should be referred for surgical evaluation. Surgery has become standard treatment for patients with resectable oligometastatic disease confined to the liver and can be curative in approximately 25% of these patients. Previous guidelines defined resectability of hepatic metastases based on the number of lesions, tumor size, and potential for clear surgical margins, but newer approaches define resectable disease as metastatic tumors that can be completely resected while leaving an adequate functional residual liver volume.

Hepatic arterial embolization (**Option A**) is a technique that can be used for control of more vascular tumors such as hepatocellular carcinoma or neuroendocrine tumors, but it is not routinely used in colorectal cancer because these tumors tend to be relatively low in vascularity. Further, such embolizations are palliative, noncurative interventions, whereas surgery has curative potential.

A needle biopsy (**Option B**) should not be done because it will not affect management. This patient's clinical presentation is compelling enough for recurrent colorectal cancer that a negative needle biopsy would be assumed to be a false-negative result, and so would not alter management, and surgical resection would be the appropriate intervention regardless of the biopsy results. A needle biopsy may be appropriate if the diagnosis is in doubt or if there is consideration for neoadjuvant chemotherapy. Consideration of neoadjuvant chemotherapy in some treatment centers is based on the potential to convert patients with an initially unresectable large volume of liver metastases to resectable disease. Although data on the frequency of success with this strategy are not available, they are probably low.

Because this patient is potentially curable, systemic chemotherapy (**Option D**), which is not curative, would not be a correct consideration.

KEY POINTS

- Postoperative surveillance following curative resection for colorectal cancer is used to identify oligometastatic disease in the liver or lung that may be resectable.
- Surgical resection is a curative option for patients with oligometastatic colorectal cancer.

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Item 42 Answer: C

Educational Objective: **Manage high-emetic-risk chemotherapy.**

This patient is anticipated to have severe nausea and vomiting from her high-emetic-risk chemotherapy and should be given ondansetron, aprepitant, olanzapine, and dexamethasone (**Option C**). There has been substantial progress in reducing chemotherapy-induced nausea and vomiting. Chemotherapeutic agents can be stratified by their emetogenic potential into high, moderate, low, and minimal risk. For patients receiving highly emetogenic chemotherapy, such as an anthracycline (e.g., doxorubicin) combined with cyclophosphamide, standard antiemetic treatments include a four-drug combination of an NK1 receptor antagonist (such as aprepitant or netupitant), a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist (such as ondansetron, granisetron, or palonosetron), dexamethasone, and olanzapine (an atypical antipsychotic). Olanzapine should be continued on days 2 to 4. These drug combinations have markedly reduced the incidence of acute emesis (in the first 24 hours) and improve the risk of delayed emesis (after 24 hours). Olanzapine, when added to standard antiemetic regimens, has been found to be effective for the treatment of delayed chemotherapy-induced nausea and vomiting (although some oncologists may not routinely prescribe this as first-line therapy due to the risk of sedation). Other examples of high-emetic-risk chemotherapeutic drugs (vomiting risk >90%) include carmustine, cisplatin, cyclophosphamide (>1,500 mg/m^2), dacarbazine, mechlorethamine, and streptozocin.

Many patients treated with moderate-emetic-risk chemotherapeutic agents (excluding higher-dose carboplatin) can be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. Certain chemotherapeutic agents in this category may cause delayed nausea and vomiting (e.g., cyclophosphamide, doxorubicin, and oxaliplatin), and in this case, patients can be offered dexamethasone on days 2 and 3.

Benzodiazepines, such as lorazepam (**Option A**), may be used as adjuncts for nausea, although they should not be used as single agents.

There is insufficient evidence regarding the value of medical marijuana (**Option B**) for chemotherapy-induced nausea. Evidence is also insufficient for recommending the use of medical marijuana in place of the tested and approved cannabinoids dronabinol and nabilone for the treatment of nausea and vomiting caused by chemotherapy or radiation therapy.

Patients treated with low-emetic-risk antineoplastic agents should be offered either a single dose of a 5-HT_3 receptor antagonist, such as ondansetron, or a single dose of dexamethasone (**Option D**). A few examples of chemotherapeutic agents with low emetic risk (10%-30%) include fluorouracil, methotrexate, and docetaxel.

KEY POINTS

- For patients receiving high-emetic-risk chemotherapy, standard antiemetic treatments include a four-drug combination of an NK1 receptor antagonist, a 5-hydroxytryptamine-3 receptor antagonist, dexamethasone, and olanzapine.
- Olanzapine, when added to standard antiemetic regimens, has been found to be effective for the treatment of delayed chemotherapy-induced nausea and vomiting.

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Item 43 Answer: B

Educational Objective: Treat hypercalcemia of malignancy.

This patient has hypercalcemia, likely due to malignancy, and should be treated urgently with intravenous isotonic saline and calcitonin (**Option B**). Hypercalcemia of malignancy occurs in 20% to 30% of patients with advanced cancer. It is most frequent in patients with myeloma and cancer of the lung, breast, kidney, head, and neck. Patients with severe or symptomatic hypercalcemia should receive isotonic saline volume expansion, which will increase renal perfusion and urine calcium excretion. The administration of isotonic saline at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour is a reasonable goal. Calcitonin increases kidney excretion of calcium and decreases bone resorption; it can decrease calcium within several hours in responsive patients. Tachyphylaxis to calcitonin may appear after 24 to 48 hours, so therapy is usually discontinued after this time period. This patient has an elevated serum creatinine level, which is a common complication of hypercalcemia, and intravenous isotonic saline may improve renal function as well.

Denosumab (**Option A**), a receptor activator of nuclear factor κB ligand inhibitor, is very effective in reducing serum calcium levels. It is typically reserved for patients who do not respond to bisphosphonate therapy. Denosumab can be used when bisphosphonate therapy is contraindicated, such as in patients with kidney failure. Patients receiving denosumab should be monitored for the subsequent development of hypocalcemia.

Furosemide (**Option C**), a loop diuretic, is not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of furosemide to avoid hypotension and further kidney injury.

Bisphosphonates (**Option D**) are effective medications for correcting hypercalcemia of malignancy and are frequently used as a key part of management. However, their maximum effect occurs in 2 to 4 days, so they are usually given in conjunction with intravenous isotonic saline. Bisphosphonates are contraindicated in the setting of kidney failure.

KEY POINTS

- Patients with severe or symptomatic hypercalcemia should receive intravenous isotonic saline to expand vascular volume, renal perfusion, and urine calcium excretion.
- Loop diuretics are not indicated in the treatment of hypercalcemia of malignancy unless kidney failure or heart failure is present; in these circumstances, intravenous expansion of vascular volume should precede the administration of loop diuretics.

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Item 44 Answer: A

Educational Objective: Treat midline poorly differentiated carcinoma of unknown primary site.

The most appropriate management is chemotherapy with a cisplatin-based germ cell regimen (**Option A**). Despite steady improvements in diagnostic and imaging techniques during the past decades, a reasonable evaluation will not identify the source of cancer in a small number (less than 5%) of all patients presenting with metastatic cancer. This heterogeneous group of patients is classified as having cancer of unknown primary (CUP). Standard evaluation of CUP includes a full medical history and physical examination and contrast-enhanced CT of the chest, abdomen, and pelvis. Histologic evaluation of the most accessible tumor mass should include a limited number of immunohistochemical stains to assess the nature of the tumor and to identify or exclude treatable histologies (such as lymphoma or germ cell tumor). Ultimately, CUP is a diagnosis of exclusion after evaluation has failed to identify the primary tumor, which may either be too small to be detected or may have been destroyed immunologically and is no longer present. The patient is a young male with a poorly differentiated CUP that is predominantly presenting in a midline distribution. In the absence of a clearly identified primary, these patients should be treated presumptively for metastatic testicular (germ cell) cancer with a cisplatin-based chemotherapy regimen. The absence of serum α-fetoprotein and β-human chorionic gonadotropin, normal testicular examination, or even normal ultrasonography does not exclude this treatment approach.

A fluorouracil-based chemotherapy regimen (**Option B**) focused on digestive tract malignancies would be an appropriate consideration for an adenocarcinoma of unknown primary that was predominantly below the diaphragm with liver and/or peritoneal involvement.

The extent of disease described makes initial treatment with either surgery or radiation therapy (**Options C, D**) inappropriate, although these modalities might be considered for consolidation therapy at a later date if a good response to chemotherapy is obtained first.

KEY POINT

- Poorly differentiated carcinoma of unknown primary site that is predominantly presenting in a midline distribution should be treated presumptively for metastatic germ cell cancer with a cisplatin-based chemotherapy regimen.

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Item 45 Answer: D

Educational Objective: Select breast cancer therapy informed by a multigene recurrence assay.

This patient with estrogen receptor (ER)–positive, human epidermal growth factor 2 (*HER2*)–negative breast cancer should have a multigene recurrence assay or gene expression profile (**Option D**), such as the 21-gene recurrence score, to inform chemotherapy decision making. If the result is low/intermediate, she should have hormone therapy alone and, if high, chemotherapy and hormone therapy. ER-positive, *HER2*-negative breast cancer risk may vary considerably based on the anatomic extent of disease (as indicated by tumor size and axillary lymph node involvement) as well as features that indicate the biology of disease, including grade and degree of ER positivity. Gene expression profiles performed on the tumor itself are independently associated with risk of recurrence and the degree of chemotherapy benefit. The Oncotype DX Recurrence Score has the highest-quality data available and is the most widely used test in the United States. Patients with node-negative, ER-positive/*HER2*-negative breast cancer and low (RS 0-10) and intermediate (RS 11-25) scores do not benefit from chemotherapy, although there remains controversy regarding the role of chemotherapy for women younger than 50 years and with an RS of 16 to 25. However, patients with a high RS (≥31) do benefit from chemotherapy. These tests have dramatically improved the ability to avoid chemotherapy for patients at low risk of recurrence who will not benefit from chemotherapy and to identify patients at greater risk and who do benefit from chemotherapy. Consensus guidelines recommend sending a gene expression profile for patients with stage II, ER-positive/*HER2*-negative breast cancer to inform chemotherapy decision making. If the results of the gene expression profile would not inform decision making (if she would not take chemotherapy regardless of the score), a gene expression profile should not be sent.

Chemotherapy followed by endocrine therapy for 5 years (**Option B**) should not be recommended to this patient without a gene expression profile to inform the decision. Most patients with ER-positive/HER2-negative breast cancer who have the 21-gene recurrence score performed have low- or intermediate-risk tumors and therefore do not benefit from adjuvant chemotherapy. Administering adjuvant chemotherapy without this information could expose the patient to unnecessary risk without the potential for benefit.

This patient will need adjuvant endocrine therapy. Chemotherapy alone (**Option A**) would be inappropriate. Endocrine therapy alone (**Option C**) may be appropriate depending on the results of the multigene recurrence assay.

KEY POINT

- For patients with hormone receptor–positive, human epidermal growth factor 2–negative breast cancers with zero to three positive axillary nodes, the use of multigene assays informs the decision regarding the need for chemotherapy.

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Item 46 Answer: A

Educational Objective: Treat metastatic non–small cell lung cancer with an *ALK* translocation with alectinib.

This patient has non–small cell lung cancer with an *ALK* translocation and should be treated with alectinib (**Option A**). Molecular alterations are playing an increasingly important role in the evaluation and treatment of patients with metastatic non–small cell lung cancer. Current evidence supports use of specific targeted agents based on identification of certain molecular alterations in tumor tissue. Such testing is a routine component of the evaluation of any patient with metastatic non–small cell lung cancer. Treatment is selected as appropriate based on the presence or absence of alterations. The patient in this case underwent such testing and was found to have a translocation involving the *ALK* gene, resulting in constitutive activation of the *ALK* tyrosine kinase. Alectinib is a tyrosine kinase inhibitor with specific activity against the *ALK* gene and has been shown to be very active in this patient population. It is a standard treatment and is recommended as front-line treatment for a patient found to have an *ALK* translocation.

The combination of chemotherapy and pembrolizumab (**Option B**) can be used as initial treatment regardless of programmed death ligand-1 expression level. However, it is indicated only in patients who do not have a driver mutation for which there is an applicable targeted therapy available. Because this patient does have a driver mutation, treatment with this combination is not recommended as first-line treatment.

Although platinum-based chemotherapy (**Option C**) is sometimes used as initial therapy before the results of mutation testing are available, this patient is already known to have an *ALK* translocation. Alectinib has been shown to improve survival compared with chemotherapy in patients with an *ALK* translocation and is the preferred therapy.

Stereotactic radiation therapy (**Option D**) is an effective treatment for patients with stage I non–small cell lung cancer who cannot tolerate surgery. Stereotactic radiation therapy is not indicated in the treatment of metastatic lung cancer.

KEY POINTS

- Testing for molecular alterations (epidermal growth factor receptor, *ALK, ROS1*) is a routine component of the evaluation of any patient with metastatic non–small cell lung cancer.
- For metastatic non–small cell lung cancer with an *ALK* translocation, initial treatment should be with alectinib.

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Item 47 Answer: D

Educational Objective: Understand the meaning of progression-free survival.

A longer time without further cancer growth (**Option D**) can be most reasonably expected with this patient's new chemotherapy regimen. *Progression-free survival* is a metric characterized as the time from when a treatment is started until the time that either the tumor progresses or the patient dies. It is therefore a measure of how long the patient will live with the disease under control, but it is not a measure of how long the patient will live (**Option C**). Progression-free survival is a term that is easily misunderstood and confused with *overall survival*. *Progression-free interval* would more accurately describe what is referred to as progression-free survival.

The one pure and simple term is *cure* (**Option A**). Cure means, as one would expect, that the cancer is gone, no further treatment is required, and the patient will live out his or her life without seeing that type of cancer again. This should not be confused with overall survival. Overall survival is the term used to describe the time from when a treatment is started until the time of patient death, and so it is a metric of how long a patient lived. Overall survival is often misunderstood by patients to be synonymous with *cure*. This misunderstanding can be further compounded by the frequent use of the phrase *significant improvement in survival*, in which *significant* refers to the statistical certainty of the finding but is often misinterpreted as a substantial improvement in survival. Many drugs have been approved with significant improvements in survival that are limited to less than 2 or 3 months, a quantity that may not be clinically significant.

Quality of life (**Option B**) is a complex metric that incorporates many physical and psychological aspects of a patient's overall condition. However, in a patient with low symptom burden such as the one described here, a drug that has added toxicity is unlikely to contribute favorably to quality of life.

KEY POINT

- Progression-free survival is the time from when a treatment is started until that treatment is no longer controlling the cancer; progression-free survival may not correlate with overall survival.

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Item 48 Answer: A

Educational Objective: Screen for osteoporosis in a patient taking an aromatase inhibitor.

The most appropriate management of this patient's bone health is to screen for osteoporosis with dual-energy x-ray absorptiometry (DEXA) (**Option A**). Bone loss occurs at an increased rate in cancer survivors who have taken long-term glucocorticoids and in women who have undergone surgical, irradiation, or chemotherapy-induced premature menopause or who are taking aromatase inhibitors such as anastrozole for breast cancer. Adverse effects of aromatase inhibitors include arthralgia, vaginal dryness, sexual dysfunction, cardiovascular events, hyperlipidemia, and higher risks of osteoporosis and fractures. Compared with tamoxifen, aromatase inhibitors have a lower risk of venous thrombosis and endometrial cancer. Up to one third of women develop aromatase inhibitor–associated symmetric arthralgia, joint stiffness, and bone pain. Assessment of bone density and treatment or prophylaxis should be considered to reduce the risk of fracture. Management commonly includes routine supplements of vitamin D and calcium (while monitoring serum calcium levels), DEXA screening for osteoporosis, and for patients with confirmed osteoporosis, bisphosphonate or denosumab therapy. Vigilance is required to detect bisphosphonate complications such as osteonecrosis of the jaw and atypical subtrochanteric spiral fractures of the femur.

Alendronate (**Option B**), a bisphosphonate, or denosumab (**Option C**), a monoclonal antibody directed against the receptor activator of nuclear factor κB ligand, could be considered if the patient is diagnosed with osteoporosis. In the absence of a bone density measurement, initiating treatment for osteoporosis is premature. Bone mineral density should be measured now, and in the absence of osteoporosis, repeated in 2 years. If the patient develops more severe osteopenia (T-score less than 2) or osteoporosis (T-score less than 2.5), then a bisphosphonate or denosumab would be appropriate.

Raloxifene (**Option D**) is in the same family as tamoxifen and works as a selective estrogen receptor modulator. It also has positive effects on bone density but is an inferior agent for breast cancer, so substituting raloxifene for anastrozole is not indicated. Raloxifene is approved for osteoporosis and for breast cancer chemoprevention in patients with high risk of breast cancer but not for adjuvant therapy of breast cancer, as is needed in this case.

KEY POINTS

- Aromatase inhibitors are associated with an increased risk of osteoporosis and fracture.
- Calcium and vitamin D supplements are recommended for patients taking aromatase inhibitors, as is screening for osteoporosis with dual-energy x-ray absorptiometry.

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Item 49 Answer: D

Educational Objective: Manage early-stage chronic lymphocytic leukemia.

For this patient with early-stage chronic lymphocytic leukemia (CLL), there is no indication for therapy, and it is safe to proceed with surgery (**Option D**). CLL is a low-grade B-cell lymphoproliferative disorder. Many patients are not symptomatic at presentation and are diagnosed when noted to have a lymphocytosis on a routine complete blood count (CBC).

Bone marrow aspiration and biopsy (**Option A**) are generally unnecessary for patients newly diagnosed with CLL. In most cases, the diagnosis is suggested by an absolute lymphocytosis on CBC with an abundance of predominantly mature-appearing lymphocytes on peripheral smear, characteristically associated with "smudge cells." The diagnosis is confirmed by flow cytometry, which shows monoclonal B cells that usually co-express CD5 (typically a T-cell marker) along with the B-cell antigens CD19 and CD20. Routinely, cytogenetics and fluorescence in situ hybridization studies are performed, along with determination of immunoglobulin variable region heavy chain (*IgVH*) status, to help confirm the diagnosis and provide prognostic information. Favorable prognostic features include the presence of del(13), absence of del(17p), and the presence of a mutated *IgVH* as opposed to unmutated status. Patients with CLL without systemic symptoms, bulky adenopathy, or significant cytopenias should not be treated.

Although chemoimmunotherapy regimens such as bendamustine or fludarabine and cyclophosphamide combined with an anti-CD20 antibody such as rituximab (**Option C**) are very active, these have been increasingly replaced by oral targeted therapies such as ibrutinib (**Option B**) (which inhibits Bruton tyrosine kinase) and venetoclax (a B-cell lymphoma 2 inhibitor). These targeted agents were initially studied in patients with CLL who had relapsed or refractory disease, but studies now support their use as first-line therapy. At this time, despite the availability of many active agents and regimens, there is no evidence that earlier institution of therapy is associated with better outcomes. Many patients will go for years, and some indefinitely, without requiring therapy for their disease.

KEY POINTS

- The diagnosis of chronic lymphocytic leukemia is suggested by absolute lymphocytosis with an abundance of predominantly mature-appearing lymphocytes on peripheral smear and confirmed by flow cytometry.
- Chronic lymphocytic leukemia is typically an indolent disease, and many patients require no therapy for many years.

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Item 50 Answer: C

Educational Objective: Treat a patient with low-risk cervical cancer who wishes to maintain fertility.

The most appropriate treatment is fertility-preserving surgery (**Option C**). This patient has early-stage and low-risk disease, and large case series have demonstrated that radical trachelectomy (in which the cervix is removed) and cervical conization are both effective procedures associated with low risks of recurrence. The choice between trachelectomy and conization is determined by depth of microscopic invasion, among other factors. Only select patients with low-risk disease are appropriate candidates for these procedures. Large series have demonstrated that pregnancy rates are approximately 50%, and many women may become pregnant spontaneously.

Concurrent radiation therapy and cisplatin (**Option A**) is recommended for patients with stage III cervical cancer but not for patients with stage I cervical cancer. This treatment is associated with greater morbidity and is reserved for patients with greater risks of locoregional and distant recurrence with higher-stage disease. Furthermore, chemoradiation is not a fertility-sparing approach, and this patient wishes to preserve fertility.

Continuous progestin therapy (**Option B**) may be used as a fertility-sparing approach for select patients with early-stage endometrial cancer but is not a treatment for cervical cancer. Cervical cancer is generally not an endocrine-sensitive cancer, and systemic therapy focuses mostly on the use of chemotherapy.

Hysterectomy and pelvic node dissection (**Option D**) is appropriate treatment for cervical cancer but does not preserve fertility. This patient could undergo a trachelectomy or cone biopsy with the aim of preserving her fertility. It is appropriate to counsel the patient about both options to inform her regarding the potential risks and benefits of each approach.

KEY POINT

- For patients with early-stage, low-risk cervical cancer, fertility-sparing surgeries are options.

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Item 51 Answer: C

Educational Objective: Evaluate metastatic gastroesophageal cancer.

The most appropriate test to perform next is assessment of the tumor for human epidermal growth factor 2 (*HER2*) amplification (**Option C**). This patient has an adenocarcinoma of the distal esophagus/gastroesophageal junction, which has metastasized to the liver and supraclavicular lymph node. Risk factors for adenocarcinoma include smoking along with gastroesophageal reflux disease (GERD) and obesity. The development of Barrett esophagus as a result of GERD, especially with dysplastic features, is a further risk for developing adenocarcinoma of the esophagus. Pain or difficulty on swallowing, weight loss, nausea, vomiting, or persistent dyspepsia may be presenting symptoms. Upper endoscopy and biopsy establishes the diagnosis. Approximately 25% of such patients will have tumors that show *HER2* amplification; such tumors achieve a superior response to chemotherapy when the anti-*HER2* monoclonal antibody trastuzumab is added to standard chemotherapy. For this reason, determination of *HER2* amplification status is necessary when initiating chemotherapy.

BRAF mutation status (**Option A**) is of paramount importance in patients with melanoma, 40% of whom will have *BRAF*-mutated tumors. These tumors are highly likely to respond to tyrosine kinase inhibitors targeting *BRAF*, but such mutations are exceedingly rare in upper gastrointestinal malignancies, and routine testing is not indicated.

Epidermal growth factor receptor (*EGFR*) mutation status (**Option B**) is relevant to the use of anti-*EGFR* tyrosine kinase inhibitors in non–small cell lung cancer; however, these agents have not been demonstrated to be active in gastrointestinal cancers and so are not part of the treatment paradigm.

A PET/CT (**Option D**) will not add useful information because the available CT scan demonstrates unequivocal metastatic disease, and any further information from the PET scan would not change the treatment approach, which will be systemic chemotherapy. Any further information regarding extent of disease that might be found on PET/CT would not be expected to change management.

KEY POINTS

- Gastroesophageal tumors should be evaluated for human epidermal growth factor 2 overexpression.
- Adding trastuzumab to chemotherapy regimens for patients with metastatic gastroesophageal tumors and human epidermal growth factor 2 overexpression provides a modest survival benefit.

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Item 52 Answer: D

Educational Objective: Treat stage I non–small lung cancer with stereotactic radiation therapy.

The most appropriate treatment for this patient's stage I non–small cell lung cancer is stereotactic radiation therapy (**Option D**). Surgery is the standard treatment for stage I and some stage II non–small cell lung cancers, and in patients treated with surgery, 5-year survival is about 60% to 70%. However, not all patients are surgical candidates. Before undergoing surgery, it is critical to perform a medical evaluation to ensure that surgery would not be associated with undue risk. That was done in this case, and it was determined that this patient was not a surgical candidate. Multiple studies have shown that stereotactic radiation therapy is an effective treatment for this patient population, with demonstrated excellent rates of local control, particularly in patients with stage I cancers. This patient, who is not fit for surgery, is a good candidate for such treatment.

Combination platinum-based chemotherapy (**Option A**) is another accepted treatment for patients with metastatic non–small cell lung cancer. However, it is not an accepted treatment for early-stage disease. Although treatment with stereotactic radiation therapy can be curative, treatment with combination chemotherapy would not be curative and is not indicated for this patient.

Combined chemotherapy and radiation therapy (**Option B**) are used commonly for the treatment of stage III non–small cell lung cancer and is an accepted treatment for this group of patients. However, it has not been shown to be of benefit in patients with stage I or stage II disease and is not indicated for treatment of this patient.

Immunotherapy (**Option C**) plays an increasingly important role in the treatment of non–small cell lung cancer. It works by reversing inhibition of the cellular immune response caused by cancers. Although it has a role in the treatment of some patients with metastatic non–small cell lung cancer, it is not a standard treatment for patients with nonmetastatic disease.

KEY POINTS

- Surgery is the standard treatment for stage I and most stage II non–small cell lung cancers.
- For patients with non–small cell lung cancer who are not candidates for surgery, stereotactic radiation therapy can be used to treat stage I cancers.

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Item 53 Answer: D

Educational Objective: Diagnose radiation-induced hypothyroidism.

The most appropriate test to perform next is measurement of thyroid-stimulating hormone (TSH) (**Option D**). This patient is at risk for radiation-induced hypothyroidism. Risk factors for radiation-induced hypothyroidism include higher doses and treatment at a younger age. Rates of hypothyroidism may approach 50%. Patients who have received radiation therapy to the thyroid may develop subclinical or clinical hypothyroidism many years or decades later. These patients are also at increased risk for thyroid cancer compared with the general population, although the overall risk remains low. Annual measurement of TSH is recommended in patients who received radiation therapy to the neck or mediastinum. An elevated TSH concentration should be followed by measurement of thyroxine to confirm the diagnosis of hypothyroidism. Other late effects of irradiation in Hodgkin lymphoma survivors can include an increased risk of breast cancer in women who receive thoracic irradiation, particularly in adolescence and early adulthood. There is also an increased risk of sarcoma and lung cancers.

Although a CT of the neck, chest, abdomen, and pelvis (**Option A**) or PET/CT (**Option C**) could be obtained if there were concern about a relapse of Hodgkin lymphoma, relapse after 7 years would be unusual and thus a less likely cause for his symptoms.

Patients who have received mantle irradiation for Hodgkin lymphoma also have a high risk of cardiac disease, including accelerated coronary artery disease, pericardial disease, and valvular disease. However, these risks for Hodgkin lymphoma survivors have likely been reduced from the past, as fewer patients receive radiation therapy and those who do have smaller fields, lower total cumulative doses, and more sophisticated treatment planning to minimize toxicities. This patient received neck, not mantle irradiation, and has no signs or symptoms of cardiovascular disease. An echocardiogram (**Option B**) is not indicated.

Although the risk of thyroid cancer is also increased after radiation therapy to the neck, the overall incidence remains low. Routine ultrasound screening (**Option E**) is not recommended, but diagnostic ultrasonography should be performed if the patient develops a palpable nodule.

KEY POINTS

- Irradiation to the neck significantly increases the risk of hypothyroidism.
- Annual measurement of serum thyroid-stimulating hormone is recommended in patients who received irradiation to the neck or mediastinum.

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Item 54 Answer: A

Educational Objective: Evaluate a patient with newly diagnosed colon cancer for metastatic disease.

A contrast-enhanced CT (**Option A**) is the most accurate and useful imaging modality for staging of patients with a new diagnosis of colon cancer. Staging with the TNM cancer staging system is the first step in treatment planning. Preoperative clinical staging begins with a history to identify localizing symptoms that may represent metastatic disease and physical examination to detect ascites, hepatomegaly, and lymphadenopathy. Laboratory evaluation includes serum carcinoembryonic antigen (CEA) in addition to routine chemical and metabolic studies. An elevated CEA level indicates a worse prognosis for patients at any stage of colon cancer compared to patients with normal levels. In addition, failure of an elevated CEA level to normalize after resection suggests the continued presence of metastatic disease and need for additional evaluation. A rising CEA level during the surveillance period after surgical resection indicates recurrent disease and the need for diagnostic imaging. Additional staging evaluation includes a full colonoscopy (if possible) and contrast-enhanced CT of the abdomen and pelvis. In addition to imaging the abdomen and pelvis, the chest should be imaged to rule out pulmonary metastases and to establish a baseline for surveillance. This staging approach is endorsed by the National Comprehensive Cancer Network.

CT colonography (**Option B**) is an alternative to colonoscopy for screening of average-risk persons without known or suspected cancer but would not add to the information that has already been obtained in this case from a standard colonoscopy.

National guidelines specifically recommend against use of whole-body PET/CT (**Option C**) for either preoperative staging or for postoperative surveillance. They have a higher than often appreciated false-positive and false-negative rate and have not been shown to improve on the accuracy of preoperative staging. In some instances, PET/CT may be useful for evaluating an equivocal finding on a contrast-enhanced CT.

Staging before definitive surgical resection is essential to preoperative planning and postoperative care, including the need for adjuvant therapy. Therefore, in nonemergent situations, staging is planned prior to surgery. To forgo staging before surgery (**Option D**) may result in suboptimal patient care.

KEY POINTS

- Staging evaluation of newly diagnosed colon cancer includes measurement of serum carcinoembryonic antigen level and contrast-enhanced CT of the chest, abdomen, and pelvis.
- PET/CT is not recommended for either preoperative staging or for postoperative surveillance in patients with colon cancer.

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Item 55 Answer: A

Educational Objective: Screen for lung cancer in a former smoker diagnosed with head and neck cancer.

This patient should have a low-dose CT of the chest in 1 year (**Option A**). She was diagnosed with locally advanced hypopharynx cancer. As is common in this type of cancer, treatment with combined chemotherapy and irradiation was recommended. She completed this treatment and achieved complete remission. Surveillance for recurrence is now indicated. Standard surveillance consists of physical examination and assessment for symptoms suggestive of recurrence. Physical examination includes in-office laryngoscopy to evaluate the upper aerodigestive tract for both local recurrence and development of second primary cancers. Following an imaging study identifying no active disease after completion of treatment, further imaging studies for surveillance purposes are not indicated. Such testing has not been shown to improve outcomes. Rather, imaging to look for recurrence is based on clinical suspicion of recurrence as directed by signs and symptoms. However, patients diagnosed with head and neck cancer are at risk for second cancers, most notably non–small cell lung cancer. This is especially true in patients aged 50 to 80 years who are current smokers or have quit less than 15 years ago and who have at least a 20-pack-year smoking history. All patients who meet criteria for lung cancer screening should be offered screening with a low-dose CT on an annual basis.

PET/CT (**Option C**) is not indicated in this patient for surveillance purposes because it does not improve outcomes. The same is true for MRI of the neck (**Option B**). Advanced imaging is reserved for patients with signs or symptoms suggestive of recurrence.

Up to 20% of head and neck cancer survivors develop a second primary cancer related to smoking and alcohol exposure. In addition to lifestyle modification, screening for lung cancer should be implemented in individuals at increased risk, rather than no additional imaging (**Option D**).

KEY POINTS

- Following an imaging study identifying no active disease after completion of treatment for head and neck cancer, further imaging studies for surveillance purposes are not indicated.
- Patients with head and neck cancer, especially current or former smokers, should be screened for lung cancer.

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Item 56 Answer: D

Educational Objective: Screen for Lynch syndrome.

All patients with a new diagnosis of colon cancer require evaluation of mismatch repair protein expression status (**Option D**). Loss of expression of mismatch repair proteins would be expected in approximately 15% of patients with colorectal cancer. Of these 15% with mismatch repair protein deficiency, approximately one in five will have a germline mismatch repair deficiency, which is known as Lynch syndrome. Patients with Lynch syndrome require more extensive surveillance for additional colorectal cancers and other malignancies. Lynch syndrome is autosomal dominant, and so identification also has important implications for family screening and surveillance. The most common cancers in Lynch syndrome are colorectal and uterine, so this patient's family history is concerning for Lynch syndrome.

BRAF and *KRAS* mutational status (**Options A, C**) are important for treatment planning in patients with metastatic colorectal cancer but have no role in the treatment decisions or management of stage I, II, or III colorectal cancer. Colon cancers harboring mutations in the *KRAS, NRAF,* or *BRAF* gene do not respond to the monoclonal antibodies cetuximab and panitumumab, and in fact, the growth of the RAS-mutated tumors may even be accelerated by these agents. Therefore, all metastatic colorectal cancers now require tumor genotyping for *KRAS*, *BRAF*, and *NRAS* mutations, and only tumors lacking all three of these mutations are appropriate for treatment with cetuximab or panitumumab.

Epidermal growth factor receptor (*EGFR*) mutational status (**Option B**) is important for the management of patients with metastatic non–small cell lung cancer but is not relevant in the management of colorectal cancer. For patients with non–small cell lung cancer who have non-squamous histology (particularly adenocarcinoma), testing for molecular alterations is mandatory. At present, it is considered standard care to test non–small cell lung cancers for mutations in the *EGFR* gene and for translocations involving *ALK* or *ROS1*. If an *EGFR* mutation is identified, initial treatment with erlotinib or osimertinib is recommended. If an *ALK* or *ROS1* translocation is identified, initial treatment with alectinib is recommended. These agents are small-molecule tyrosine kinase inhibitors that are specific for those genetic alterations.

KEY POINT

- All patients with a new diagnosis of colon cancer require evaluation of mismatch repair protein expression status.

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Item 57 Answer: E

Educational Objective: Evaluate cancer prognosis.

Tumor stage (**Option E**) is usually the most important prognostic factor in determining a patient's outcome. All tumors are staged using the American Joint Commission on Cancer staging system. This involves the TNM system, in which the extent of the tumor (size and/or depth of penetration), nodes (number of local-regional nodes that contain cancer), and metastases (present or absent) are considered. TNM scorings are placed on a scale of stage I though IV, with stage I having the best prognosis and stage IV the worst.

Poorly differentiated tumors (**Option A**) have, in general, a worse prognosis than well-differentiated tumors; however, this too is a modest prognostic factor compared with staging.

Although molecular profiling for driver mutations in genes such as *KRAS*, *NRAS*, and *BRAF* (**Option B**) may influence prognosis and may have implications for chemotherapy selections in advanced disease, they have far less influence on outcome than tumor stage. In addition, they are not relevant in the management of stage I colon cancer, which has a very favorable prognosis and would not require further therapy after surgery.

Performance status (**Option C**), which is a designation of the overall medical wellness, or lack thereof, of the patient may have important prognostic implications within a particular stage of disease but is far less significant prognostically than the staging itself. It is important to differentiate patients with a poor performance status who are debilitated due to chronic comorbidities from patients who would otherwise be medically fit but are acutely debilitated by their cancer. The latter situation may warrant an attempt at aggressive treatment because reversing the cancer process is the only option that will improve the patient's overall condition, whereas the former may need to be treated with less aggressive treatment or possibly no specific anticancer treatment.

Tumor size (**Option D**) may be a component of the "T" stage, but by itself, it has only modest prognostic significance relative to overall stage.

KEY POINT

- Staging is generally the most accurate prognostic indicator and largely dictates the therapeutic strategy for patients with cancer.

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Item 58 Answer: D

Educational Objective: Treat stage I rectal cancer.

The most appropriate treatment is surgery (**Option D**). Based on the results of clinical staging, this patient has a T2N0, stage I cancer of the upper third of the rectum. If pathology following surgery confirms these preoperative findings, then no further therapy would be warranted. Therefore, for stage I rectal cancer, surgery alone is the preferred initial management. With the tumor located 10 cm from the anal verge, the surgical procedure of choice would be a low anterior resection, performed with the total mesorectal excision technique, with either a direct anastomosis, or, more likely, a temporary diverting ileostomy, which would be reversed after 2 to 3 months. Such a resection would be anticipated to be sphincter-sparing, and so the patient should not require a permanent colostomy. After therapy, patients with rectal cancer should be evaluated at approximately 6-month intervals for up to 5 years with a history, physical examination, and serum carcinoembryonic antigen level assessment. Contrast-enhanced CTs of the chest, abdomen, and pelvis are typically obtained annually for 5 years.

If postoperative findings upstage the tumor to stage II or III, then there may be a need to consider further interventions such as irradiation and/or chemotherapy (**Options A, B**). Evidence is insufficient to define an optimal sequencing of the three treatment modalities, although total neoadjuvant therapy in which all planned chemotherapy and irradiation is given before surgery, is becoming a more widespread practice. Capecitabine, an oral prodrug that is converted into 5-fluorouracil (5-FU), or, less commonly, intravenous 5-FU, is given concurrently with radiation therapy (**Option C**). However, data do not support a role for adding either chemotherapy or radiation therapy to the management of surgically confirmed stage I rectal cancer.

KEY POINTS

- Rectal cancers that do not penetrate the full thickness of the bowel wall and do not involve regional lymph nodes are stage I and are treated with surgical resection.
- Patients with treated rectal cancer are evaluated at 6-month intervals with a history, physical examination, and serum carcinoembryonic antigen level assessment and annual contrast-enhanced CTs of the chest, abdomen, and pelvis; surveillance is continued for 5 years.

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Item 59 Answer: A

Educational Objective: Manage a patient with superior vena cava syndrome.

This patient has superior vena cava (SVC) syndrome and should undergo a tissue biopsy (**Option A**) to guide further management. Most cases of SVC syndrome are caused by malignancies with large mediastinal masses. Patients typically present with edema of the head, neck, and arms, often with cyanosis, plethora, and distended cutaneous collateral vessels. They may have headache, cough, dyspnea, hoarseness, or syncope. Most patients do not require emergency intervention. Treatment of patients presenting with SVC syndrome should be guided by the underlying malignancy. Although local therapies directed at mediastinal masses may yield symptomatic improvement, this may compromise treatment for the underlying disease. In this patient, the enlarged right supraclavicular lymph node is easily accessible for surgical biopsy with minimal risk. Many patients with SVC syndrome have highly chemotherapy-sensitive malignancies, such as small cell carcinoma of the lung or aggressive non-Hodgkin lymphoma. Even those who present with a heavy burden of symptoms or vital sign abnormalities such as hypoxia may be treated with standard chemotherapy to obtain shrinkage of the tumor and improvement in SVC syndrome.

Glucocorticoids (**Option B**) should not be administered routinely to patients with SVC syndrome. Pretreatment with glucocorticoids can obscure the tissue diagnosis, particularly for patients with aggressive lymphomas, which may be very sensitive to glucocorticoids. These patients may benefit from glucocorticoids as part of the initial treatment regimen following tissue diagnosis.

Radiation therapy (**Option C**) should only be performed after a tissue diagnosis is obtained and if it is otherwise indicated for management of the underlying disease. Radiation therapy may be used if the patient has highly symptomatic SVC syndrome in the setting of a malignancy that is unlikely to respond quickly to systemic therapy, or if the patient is not fit to receive systemic therapy.

Surgical resection of the mediastinal adenopathy (**Option D**) to relieve SVC syndrome is not appropriate in this patient because treatment should be tailored to the underlying malignancy. The supraclavicular node is amenable to biopsy with less operative risk.

KEY POINTS

- Most cases of superior vena cava syndrome are caused by malignancies with large mediastinal masses, and most patients do not require emergency intervention.
- For superior vena cava syndrome, a tissue biopsy should be obtained to determine the underlying malignancy and guide further management.

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Item 60 Answer: B

Educational Objective: Prevent breast cancer with an aromatase inhibitor in a high-risk woman with previous deep venous thrombosis.

The most appropriate breast cancer chemoprevention for this patient is exemestane (**Option B**). The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects. This recommendation applies to asymptomatic women 35 years and older, including patients with previous benign breast lesions on biopsy (such as atypical ductal or lobular hyperplasia and lobular carcinoma in situ). This recommendation does not apply to women who have a current or previous diagnosis of breast cancer or ductal carcinoma in situ. A variety of tools, including the Gail Model Risk Assessment Tool (www.cancer.gov/bcrisktool), provide decision support in estimating the risk of breast cancer. The USPSTF advises against using any hard cut-off point for defining increased risk but suggests focusing instead on each woman's values and priorities in weighing the reduced risk of breast cancer with increased likelihood of adverse effects.

Aspirin (**Option A**) has been explored as a breast cancer chemoprevention strategy, but its use is not established and should not be used outside of a clinical trial.

Tamoxifen, raloxifene, and the aromatase inhibitors exemestane and anastrozole reduce invasive breast cancer in women without preexisting breast cancer but do not reduce breast cancer–specific or all-cause mortality (**Options C, D**). Tamoxifen is effective in the chemoprevention of breast cancer in both pre- and postmenopausal women and reduces the risk of breast cancer by approximately 30%. Tamoxifen is associated with a significantly increased risk of venous thromboembolism (VTE) and has a black box warning for use among patients with a previous history of VTE. Raloxifene, effective in breast cancer chemoprevention for postmenopausal women, also increases the risk of VTE, although not to as great an extent. Both drugs should be avoided in women with prior VTE if there are suitable alternatives. Exemestane is an option for chemoprevention of breast cancer in postmenopausal women with a previous history of VTE. Exemestane is not associated with an increased risk of VTE.

KEY POINTS

- Tamoxifen, raloxifene, and the aromatase inhibitors exemestane and anastrozole reduce invasive breast cancer in women without preexisting breast cancer but do not reduce breast cancer–specific or all-cause mortality.
- Exemestane may be used as a preventive measure in women who are at high risk of breast cancer with a previous history of venous thromboembolic disease.

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Item 61 Answer: D

Educational Objective: **Treat well-differentiated pancreatic neuroendocrine tumor.**

The most appropriate management is repeat imaging in 3 months (**Option D**). This patient has an incidental finding of a well-differentiated, low-grade, gastrointestinal neuroendocrine tumor with multiple metastases to the liver. These tumors are often asymptomatic and indolent, and asymptomatic patients may do well with minimal growth and no symptoms for years without intervention. As such, there is no urgency to intervene, and it is beneficial to evaluate the pace of the disease before making a decision regarding whether to treat. Follow-up examination and imaging at approximately a 3-month interval is appropriate in asymptomatic patients with relatively modest-volume, asymptomatic disease. Approximately one third to one half of metastatic gastrointestinal neuroendocrine tumors will elaborate serotonin, a hormone that causes “carcinoid syndrome” with diarrhea and/or facial flushing; however, most patients have a hormonally nonfunctional tumor and so will not require treatment for these symptoms. In patients who have stable disease at the 3-month scan, further monitoring with serial imaging at 3- to 6-month intervals is appropriate.

Hepatic arterial embolization (**Option A**) is a procedure that may be helpful in shrinking liver metastases or reducing hormonal output from functional tumors. It may be appropriate in a patient with progressive, bulky, or symptomatic disease.

For moderate progression, a somatostatin analogue (**Option B**) can be used. This treatment often slows disease progression, although actual tumor shrinkage is rare. Somatostatin analogues are highly effective in controlling hormonal disease and should be given if hormone-related symptoms are present.

Peptide-receptor radiotherapy (**Option C**) is a treatment that is appropriate for patients with either a substantial disease burden or clinically significant growth under observation but would not be warranted in an asymptomatic patient with small-volume disease.

Cytotoxic chemotherapy (**Option E**) is of limited utility in patients with well-differentiated neuroendocrine tumors.

KEY POINTS

- Well-differentiated neuroendocrine tumors are indolent, frequently discovered incidentally, and often initially only require observation and serial imaging.
- Somatostatin analogues are highly effective in controlling hormonal manifestations of gastrointestinal neuroendocrine tumors and should be given if hormone-related symptoms are present.

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Item 62 Answer: A

Educational Objective: **Treat locally advanced rectal cancer.**

The most appropriate treatment for this patient is chemotherapy followed by irradiation and then surgery (**Option A**). This patient has a tumor in the proximal third of the rectum. The tumor is bulky and involves the full thickness through the rectal wall, with bulky perirectal adenopathy. This is a stage III rectal cancer, and optimal standard management would involve the use of all three modalities: chemotherapy, radiation therapy, and surgery. Clinical trials have shown that use of irradiation after surgery has greater toxicity and a higher risk of tumor recurrence in the irradiated field than when irradiation is given before surgery. Whereas a more traditional and still acceptable approach would be to use irradiation followed by surgery and then plan to give chemotherapy afterward, current practice is shifting toward the concept of total neoadjuvant therapy, in which both irradiation and chemotherapy are completed before surgery. Clinical trials have established that 5-fluorouracil given by protracted intravenous infusion or capecitabine is an equally acceptable chemotherapeutic option to be given concurrently with radiation therapy. Careful observation without surgery is becoming more widely accepted as a possible alternative strategy in patients who have a complete clinical response by examination and MRI after chemotherapy and irradiation.

Patients with rectal tumors that are not full thickness and do not have lymph node involvement (stage I) on pretreatment imaging usually undergo surgery (**Option B**); a total mesorectal excision is the preferred procedure. The mesorectum is a fatty sheath covering the rectum that contains the regional lymph nodes. A total mesorectal excision entails a sharp dissection of the pelvis outside of the mesorectum to allow removal of the mesorectum fully intact en bloc with the rectum. If local lymph node metastases or full-thickness tumor penetration is found after surgery in patients thought to be stage I preoperatively, then postoperative chemotherapy and irradiation therapy are indicated.

Surgery followed by irradiation (or by irradiation and chemotherapy) (**Options C, D**) is avoided when feasible because of greater toxicity and a higher risk of tumor recurrence in the irradiated field than when irradiation is given before surgery.

KEY POINTS

- Full-thickness rectal tumors (stage II) and/or those with involved lymph nodes (stage III) routinely require irradiation, chemotherapy, and surgery.
- Surgery followed by irradiation is avoided when feasible for rectal tumors because of greater toxicity and a higher risk of tumor recurrence in the irradiated field than when irradiation is given before surgery.

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Item 63 Answer: B

Educational Objective: Treat a patient with spinal cord compression due to metastatic cancer.

This patient has epidural spinal cord compression, and treatment with dexamethasone, surgical resection, and irradiation (**Option B**) is associated with the highest likelihood of ambulation. Spinal cord compression occurs in 2.5% of patients with metastatic cancer and may impair lower extremity strength and ambulation. The most common types of cancer that cause epidural spinal cord compression in adults are lung, breast, and prostate cancer, as well as myeloma and lymphoma. Approximately 85% of epidural spinal cord compression cases are caused by epidural extension from vertebral body metastases. Lymphomas are more likely to involve a paraspinal mass that extends through the neural foramina to cause cord compression. Pain, often worse with recumbency, is present in more than 80% of patients and usually precedes neurologic symptoms by several weeks. The patient's neurologic status at diagnosis is the most important predictor of outcome. Of patients who are able to walk when starting treatment, 80% remain ambulatory; however, less than 20% of nonambulatory patients regain the ability to walk. Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and urgent surgical decompression, followed by irradiation for most tumor types.

Patients are initially treated with glucocorticoids (**Option A**) at either a moderate or high dose if paraparesis or paraplegia is present, but there is a time-limited duration of benefit. More definitive therapy will be needed.

Certain radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression and instead may be treated urgently with irradiation alone (**Option C**). However, metastatic lung cancer should be treated with both surgery and radiation therapy if amenable to surgery and for a patient with a good prognosis, particularly in this patient with good functional status before this event.

Postsurgical irradiation is required to achieve optimal local tumor control. Surgery followed by irradiation increases the likelihood of ambulation compared with irradiation therapy alone. Glucocorticoids supplement both surgical and radiation treatment and are associated with a rapid reduction in spinal cord edema, pain, and weakness. Surgery without glucocorticoid treatment (**Option D**) is not recommended for patients with acute malignant spinal cord compression.

KEY POINTS

- Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and urgent surgical decompression, followed by irradiation for most tumor types.
- Spinal cord compression from radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression and instead, patients may be treated urgently with radiation therapy alone.

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Item 64 Answer: E

Educational Objective: Diagnose renal cell cancer in a patient with secondary erythrocytosis.

The most likely diagnosis is renal cell carcinoma (**Option E**). This patient has secondary erythrocytosis defined by the presence of erythrocytosis and an elevated erythropoietin level. Secondary erythrocytosis may be due to a variety of conditions including systemic hypoxia, high altitude, chronic carbon monoxide exposure, and renal artery stenosis. It may also be caused by autonomous production of erythropoietin independent of hypoxemia, such as a paraneoplastic syndrome. Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases (known as Stauffer syndrome), fever, hypercalcemia, AA amyloidosis, thrombocytosis, polymyalgia rheumatica, and erythrocytosis. Many of these conditions can improve with resection of the primary tumor, metastatic sites, or both. An abdominal ultrasound will likely reveal a renal mass that may have sonographic features pathognomonic for renal cell carcinoma. If the ultrasound is equivocal, CT should be performed, typically revealing findings specific enough for renal cell cancer to avoid the need for a confirmatory biopsy.

Lung cancer (**Option A**) may be associated with a variety of paraneoplastic syndromes, including hypercalcemia and the syndrome of inappropriate antidiuretic hormone secretion, but it has not been associated with ectopic erythropoietin production and would not be expected to cause hematuria.

Myelodysplastic syndrome (**Option B**) is a stem cell disorder that results in ineffective hematopoiesis and various cytopenias, the most common of which is anemia, often macrocytic. Myelodysplastic syndrome is not a cause of erythrocytosis.

Polycythemia vera (**Option C**) is a myeloproliferative disorder that is caused by a mutation in the *JAK-2* gene. This disorder results in unregulated blood cell production. Although erythrocytosis may be most striking, leukocytosis and thrombocytosis are often seen as well. Physical findings include hepatosplenomegaly. The dysregulated erythrocyte production and erythrocytosis cause a marked reduction in erythropoietin secretion. Hematuria would not be expected.

Relative erythrocytosis (**Option D**) occurs in patients who have intravascular volume contraction, often in the setting of diuretic use. These patients are characteristically obese, have hypertension, and smoke cigarettes. Relative erythrocytosis would not cause the dramatic hemoglobin elevation seen in this patient and would not explain the hematuria.

KEY POINTS

- Secondary polycythemia is the presence of erythrocytosis and an elevated erythropoietin level.
- Secondary polycythemia is commonly caused by hypoxemia but may be due to a paraneoplastic syndrome, such as that associated with renal cell carcinoma.

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Item 65 Answer: D

Educational Objective: Diagnose a patient with an ovarian mass.

This patient appears to have stage I ovarian cancer (confined to the ovary) and should therefore be referred to a gynecologic oncologist for surgical removal of the mass (**Option D**). Removal of the tumor intact is associated with improved survival. The patient should undergo comprehensive surgical staging to evaluate for additional disease that would upstage the patient. This procedure is usually performed through a laparotomy and involves inspection of the peritoneal cavity including the paracolic gutters, dome of the diaphragm, lymph node sampling, omentectomy, and peritoneal washings. Gynecologic oncologists are more likely to optimally cytoreduce patients with ovarian cancer than those without specific training in gynecologic oncology.

BRCA1/2 testing (**Option A**) is recommended for all patients with ovarian cancer, but the first step in this patient's evaluation is to establish a diagnosis.

CT-guided biopsy (**Option B**) should not be performed for an isolated adnexal mass, in part to avoid rupture of the tumor, and instead a surgical procedure should be performed to resect the tumor intact and to perform comprehensive staging. A CT-guided biopsy is an appropriate diagnostic procedure for a patient who presents with advanced ovarian cancer in which there is radiographic evidence of spread in the peritoneum or to a distant site, and which is not amenable to surgical resection. In this case, the patient may undergo an initial biopsy followed by neoadjuvant chemotherapy to facilitate optimal debulking surgery.

According to recent guidelines by the American Society of Clinical Oncology and Society of Gynecologic Oncology, patients with stage IIIC or IV ovarian cancer who are at high perioperative risk or who have a low likelihood of optimal tumor debulking should receive neoadjuvant chemotherapy (**Option C**) followed by reevaluation for cytoreductive surgery. Tumors that involve the porta hepatis, have metastasized to the liver or lungs, or that cause massive ascites are examples of disease that might be best treated with neoadjuvant chemotherapy. This patient appears to have an isolated adnexal mass, which is best treated with surgical removal by a gynecologic oncologist.

KEY POINTS

- *BRCA1/2* testing is recommended for all patients with ovarian cancer.
- Surgical exploration is recommended for diagnosis of early ovarian cancer; removing the ovarian cancer intact without rupture improves survival.

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Item 66 Answer: A

Educational Objective: Manage a patient presenting with a neck mass.

The most appropriate management at this time is fine-needle aspiration (FNA) (**Option A**). This patient, who presents with a painless, rapidly developing, partially cystic neck mass, should be considered to have squamous cell carcinoma until proven otherwise. Based on this patient's presentation, the most appropriate initial management is FNA. FNA is very accurate for diagnosis of squamous cell carcinoma and is preferred over more invasive biopsy techniques. It has a diagnostic accuracy of 88% to 89% and can be done rapidly in the office with limited or no morbidity. A more invasive form of biopsy would only be needed if

FNA results were nondiagnostic. If found to be squamous cell carcinoma, this cancer should also be evaluated for human papilloma virus (HPV) infection, as this patient is in the appropriate age range for HPV-related squamous cell carcinoma, and a largely cystic mass on CT imaging is characteristic for this infection-related cancer. HPV-related cancers occur most commonly between ages 40 to 59 years. Although HPV status does not have an impact on treatment decisions, it is associated with an improved prognosis.

Observation (**Option B**) would not be appropriate in this case. This patient has a clearly abnormal neck mass based on imaging. Prompt evaluation with FNA is necessary based on the high likelihood of cancer.

PET/CT (**Option C**) would be indicated for staging once head and neck cancer is diagnosed. However, this patient has not yet been diagnosed with head and neck cancer. PET/CT is not indicated before a diagnosis of cancer, and the results of a PET/CT scan would not change the need to biopsy this mass. Although this mass would be expected to have increased fluorodeoxyglucose uptake, some largely cystic metastatic nodes are not very avid on PET/CT, raising risk of a false-negative finding.

Surgical removal (**Option D**) might be indicated for this patient as a component of treatment for head and neck cancer. However, FNA is a much more efficient and less morbid diagnostic test. Surgery is not needed for diagnostic purposes, as squamous cell carcinoma can easily be diagnosed based on FNA results.

KEY POINT

- Fine-needle aspiration is the initial step in evaluating a neck mass suspicious for head and neck cancer.

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Item 67 Answer: A

Educational Objective: Treat a patient with stage I human epidermal growth factor receptor 2–positive breast cancer.

This patient should be treated with chemotherapy and anti-human epidermal growth factor receptor 2 (*HER2*) therapy, breast irradiation, and endocrine therapy (**Option A**). This patient has had breast-conserving surgery and as a result needs postsurgical irradiation. Postsurgical irradiation decreases both the risk of local recurrence and the risk of distant metastases, and it increases overall survival. Whereas older women with small estrogen receptor (ER)–positive/*HER2*-negative tumors may consider omission of radiation therapy, *HER2* positivity is a risk factor for local recurrence, and radiation therapy is recommended in this setting. Endocrine therapy is associated with a 40% reduction in risk of recurrence, and tamoxifen or an aromatase inhibitor is recommended for postmenopausal women with ER-positive breast cancer. Adjuvant chemotherapy combined with *HER2*-targeted treatment, such as the monoclonal antibody trastuzumab, is recommended for *HER2*-positive cancers. Women with small *HER2*-positive breast cancers can be treated with weekly paclitaxel and trastuzumab, and in this setting, outcomes are excellent with a risk of distant recurrence under 2% and a very favorable toxicity profile.

Adjuvant endocrine therapy alone or combined with radiation therapy (**Options B, D**) will not provide the same benefit of reducing the risk of recurrence or improving survival as does the combination of irradiation, chemotherapy, *HER2*-targeted therapy, and endocrine therapy for this patient. Although older patients may experience more adverse effects, treatment should not be omitted in the absence of comorbid conditions (severe cardiomyopathy) that would preclude anti-*HER2* therapy.

Gene expression profiles such as the Oncotype DX Recurrence Score (**Option C**) are not used to inform treatment decision making for patients with *HER2*-positive breast cancer. The Recurrence Score is used to determine which patients with ER-positive/*HER2*-negative breast cancer benefit from chemotherapy. Patients with node-negative ER-positive/*HER2*-negative breast cancer and low or intermediate risk Recurrence Scores generally do not benefit from chemotherapy, whereas patients with high-risk Recurrence Scores generally do benefit from chemotherapy. *HER2*-positive breast cancer itself is associated with a higher risk of recurrence but also with substantial benefit from chemotherapy and anti-*HER2* therapy (trastuzumab).

KEY POINT

- Adjuvant chemotherapy combined with human epidermal growth factor receptor 2 (*HER2*)–targeted treatment, such as the monoclonal antibody trastuzumab, is recommended for *HER2*–positive breast cancers.

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Item 68 Answer: D

Educational Objective: Manage prostate-specific antigen–only recurrent prostate cancer.

This patient has a prostate-specific antigen (PSA)–only recurrence of prostate cancer, and the most appropriate management is to monitor PSA level without treatment (**Option D**). Men treated with radiation therapy rarely achieve an undetectable PSA, as is commonly seen after surgery. Rather, the PSA will fall with treatment and reach a nadir. PSA-only recurrence is defined as an increase in the PSA level by at least 2 ng/mL (2 µg/L) above the postradiation therapy nadir. This patient had a nadir PSA of approximately 1 ng/mL (1 µg/L) and now has a PSA of 3.2 ng/mL (3.2 µg/L) 9 years after treatment. Imaging studies did not reveal any evidence of metastatic disease. Therefore, he has a PSA-only recurrence. Treatment for patients with PSA-only recurrence is informed by the degree of PSA elevation and the rate of rise in the PSA level. For men with a rapid doubling time, defined as 10 months or less, treatment is generally recommended. Standard treatment in this setting is an androgen receptor blocker (such as enzalutamide). Men with a slow PSA doubling time (for example, more than 10 months) do not require immediate treatment, however, as it can take years for them to develop clinical metastatic disease. They can be monitored with serial PSA assessment, and treatment can be deferred.

Androgen deprivation therapy (**Option A**) is not indicated in this case, given the slow PSA doubling time and the absence of biopsy-positive recurrent or metastatic disease.

Chemotherapy (**Option B**) with docetaxel is reserved for treatment of men with symptomatic metastatic disease. This patient does not have metastatic disease and has no symptoms. There is no reason to subject him to the toxicity of chemotherapy when he does not require treatment.

Cryotherapy (**Option C**) is not indicated in this case. This patient underwent transrectal ultrasound-guided biopsy to assess for focal lesions in the prostate amenable to local therapy. Given that biopsy result was negative, there is no role for cryotherapy or other local treatment to the prostate.

KEY POINTS

- Patients with prostate-specific antigen (PSA)–only recurrence of prostate cancer and a slow PSA doubling time do not require immediate treatment.
- Many patients with PSA-only recurrent prostate cancer can be monitored with serial PSA assessment.

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Item 69 Answer: A

Educational Objective: Treat *BRAF*-nonmutated melanoma with immunotherapy.

This patient has *BRAF*-nonmutated melanoma, and the best treatment is immunotherapy with an anti–CTLA-4 antibody plus an anti–programmed death (anti–PD-1) antibody (**Option A**). Ipilimumab is an anti–CTLA-4 antibody, and nivolumab is an anti–PD-1 antibody. Individually, they each have activity against malignant melanoma. Ipilimumab has a response rate as a single agent of 10% to 15%. Nivolumab and other anti–PD-1 antibodies, such as pembrolizumab, have a response rate of about 40%. The combination is more active than either drug alone, although it is associated with more immune toxicities. This immunotherapy combination is effective whether the melanoma is *BRAF* mutated or not. Some of these responses are quite durable with a minority of patients remaining free of recurrence for many years.

Although about 50% of melanomas have a *BRAF* mutation (most commonly *BRAF* V600E or V600K), the other half of melanomas do not. Patients who have a *BRAF* mutation may respond to therapy with *BRAF* inhibitors (vemurafenib, dabrafenib, and encorafenib) along with *MEK* inhibitors (trametinib, cobimetinib, and binimetinib). However, *BRAF* inhibitors are not effective in patients with tumors such as this one that is not *BRAF* mutated (**Option B**). Thus, there is no role for the use of a *BRAF* inhibitor in this patient who lacks a *BRAF* mutation. Other driver mutations identified in patients with melanoma include *NRAS* and c-KIT.

MEK inhibitors (**Option D**) do have single-agent activity in melanoma but are usually used in combination with *BRAF* inhibitors. Adding a *MEK* inhibitor to a BRAF inhibitor improves the response rate and the durability of response in *BRAF*-mutated melanoma. A *MEK* inhibitor combined with a *BRAF* inhibitor (**Option C**) is not indicated in this patient with a tumor that lacks a *BRAF*-related mutation. Finally, treatment with an anti–CTLA-4 antibody plus an anti–PD-1 antibody results in superior clinical outcomes compared to treatment with *MEK* inhibitor monotherapy.

In a patient with metastatic disease who has a *BRAF* mutation, treatment with either immunotherapy or *BRAF*-targeted therapy would be appropriate without a clear indication as of yet which treatment is superior. In patients who are ill and in need of a rapid response or in those with underlying autoimmune disorders who would be at increased risk for adverse immune-related events, *BRAF*/*MEK* inhibition may be favored, given the potential for more rapid response and the lower rate of autoimmune complications.

KEY POINTS

- Immunotherapy with an anti–CTLA-4 antibody plus an anti-programmed death antibody improves response rates compared with either agent alone and is the preferred treatment for patients with metastatic melanoma without a *BRAF* mutation.
- In a patient with metastatic melanoma with a *BRAF* mutation, treatment with either immunotherapy or *BRAF*-targeted therapy is appropriate.

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Item 70 Answer: D

Educational Objective: Treat a patient with ductal carcinoma in situ following bilateral mastectomy.

No adjuvant treatment is recommended following bilateral mastectomy as treatment for ductal carcinoma in situ (DCIS) (**Option D**). After bilateral mastectomy for DCIS, neither radiation therapy nor hormonal therapy provides benefit. DCIS is a preinvasive proliferative growth and does not have the ability to metastasize outside of the breast. Treatment is aimed at reducing the risk of local recurrences, of which half are DCIS and half are invasive cancers, the latter of which have the ability to metastasize. Surgical excision is the primary treatment for patients with DCIS and may include either mastectomy, in which the tumor along with essentially all of the normal breast tissue are removed, or lumpectomy, in which just the tumor itself is removed, ensuring a negative margin. There is no difference in long-term survival between the two operative approaches.

Irradiation (**Option B**) is not recommended in the setting of DCIS following mastectomy because the risk of local recurrence is so low. After lumpectomy, some women may benefit from adjuvant radiation therapy to decrease the risk of local recurrence.

Following lumpectomy, adjuvant hormone therapy is offered to patients with estrogen receptor–positive DCIS to reduce the risk of local recurrence; however, endocrine therapy has no impact on overall survival in this setting. After mastectomy for DCIS, adjuvant hormone therapy reduces the risk of a new primary breast cancer in the contralateral breast, and benefits should be weighed against the potential drug-related adverse effects. Tamoxifen (**Option C**) is effective in both pre- and postmenopausal women. The aromatase inhibitors letrozole and anastrozole (**Option A**) are not effective in premenopausal women. For postmenopausal women, aromatase inhibitor therapy provides superior results as an alternative to using tamoxifen alone.

Some patients with DCIS choose prophylactic bilateral mastectomy rather than hormone therapy to prevent a future primary breast cancer despite a documented lack of a survival benefit. There is no role for adjuvant hormone therapy in patients with DCIS after bilateral mastectomy.

KEY POINTS

- Neither radiation therapy nor hormonal therapy provides benefit after bilateral mastectomy for patients with ductal carcinoma in situ.
- After lumpectomy, adjuvant hormone therapy is offered to patients with estrogen receptor–positive ductal carcinoma in situ to reduce the risk of local recurrence; however, endocrine therapy has no impact on overall survival in this setting.

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Item 71 Answer: C

Educational Objective: Treat limited-stage small cell lung cancer with prophylactic cranial irradiation.

The most appropriate management for this patient would be prophylactic cranial irradiation (**Option C**). Patients with small cell lung cancer have a high risk of developing brain metastases (prophylactic cranial irradiation [PCI]). Given that risk, initial staging should include brain MRI. Following completion of treatment for patients with either extensive or limited-stage small cell lung cancer, the risk of developing brain metastatic lesions remains significant, occurring in up to two thirds of patients following attainment of complete remission with initial treatment. Given this significant risk, PCI has been studied extensively as a means of reducing the risk of brain metastases. PCI refers to radiation treatment given to the whole brain in a patient without brain metastatic disease after the completion of planned cancer treatment. Many studies have addressed use of this treatment, and a meta-analysis of 12 different trials including more than 1500 patients showed that treatment with PCI resulted in a significant reduction in the incidence of brain metastases as well as a significant reduction in mortality (this last benefit was only clearly shown for patients with limited-stage disease). Based on these benefits, this is considered a standard component of treatment for patients with either limited or extensive-stage disease who have responded to their initial therapy. Since this treatment was initially pioneered, safety concerns regarding cognitive impairment have been noted, although more modern studies have found that this risk can be mitigated with a lower total dose and a lower fraction dose.

Maintenance chemotherapy (**Option A**) is commonly used in patients with metastatic non–small cell lung cancer and has been shown to improve progression-free survival in patients who have a favorable response to their initial treatment regimen. It has no established role in the treatment of patients with small cell lung cancer.

PET/CT imaging (**Option B**) is not a standard test for surveillance following completion of treatment for small cell lung cancer. Standard surveillance consists of history and physical along with periodic chest imaging. Given lack of evidence that PET/CT can improve outcomes when used for surveillance, it is not recommended for this indication.

At the present time, this patient is doing very well and has no signs or symptoms of an active pulmonary process. CT imaging has effectively evaluated the status of her cancer. There is no indication for a repeat bronchoscopy (**Option D**).

KEY POINTS

- Prophylactic cranial irradiation reduces the incidence of brain metastases in patients with either limited or extensive-stage small cell lung cancer who have responded to their initial therapy.
- Prophylactic cranial irradiation improves overall survival in patients with limited-stage small cell lung cancer who have responded to their initial therapy.

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Item 72 Answer: D

Educational Objective: Manage low-risk melanoma with appropriate posttreatment surveillance.

This patient had low-risk (thin) melanoma (Breslow depth less than 0.8 mm) and should have a general physical examination and dermatologic evaluation every 6 months (**Option D**). Particular attention should be directed to the primary resection site for evidence of local recurrence (satellite lesions), in-transit metastases (looking for disease traveling along the course of draining lymphatics), and regional nodal involvement. Regional lymph node ultrasound can be performed to better assess for adenopathy in patients with an equivocal lymph node examination. The patient should also be carefully assessed for the development of second primary melanomas, as patients who have had one melanoma have a significantly higher risk of developing second primary melanomas. Furthermore, patients should be educated to perform routine skin self-examinations to screen for both recurrence and for new primary lesions.

Breslow staging indicates the depth of invasion of the melanoma below the surface of the skin. The risk of recurrence increases as the depth of invasion increases. Ulceration at presentation and high mitotic rate are also associated with a higher risk of recurrence. Melanoma can be a very aggressive cancer and can metastasize widely, but if caught early, it has a very high cure rate. In patients such as this one (stage I, cT1aN0 indicating a depth of invasion less than 0.8 mm), the overall cure rate is approximately 95%.

In the absence of signs or symptoms of recurrence, routine laboratory evaluation (**Option C**) or imaging with chest radiograph (**Option A**), PET/CT, or brain MRI (**Options B, E**) have a very low yield and are not routinely recommended. However, in patients with higher stages of disease (stage IIB-IV), serial imaging with CT or whole-body fluorodeoxyglucose-PET with or without brain MRI may be considered appropriate for 3 to 5 years.

KEY POINT

- Patients with low-risk (thin) melanoma should be encouraged to perform skin self-examinations as well as receive skin evaluations by a dermatologist regularly for life.

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